XXIV CONGRESSO NAZIONALE
AIRO2014
Padova, 8-11 novembre

SIMPOSIO AIRO-AIOM

Trattamenti sistemici e radioterapia nel carcinoma prostatico

Quali indicazioni? Quali farmaci?

Francesco Massari

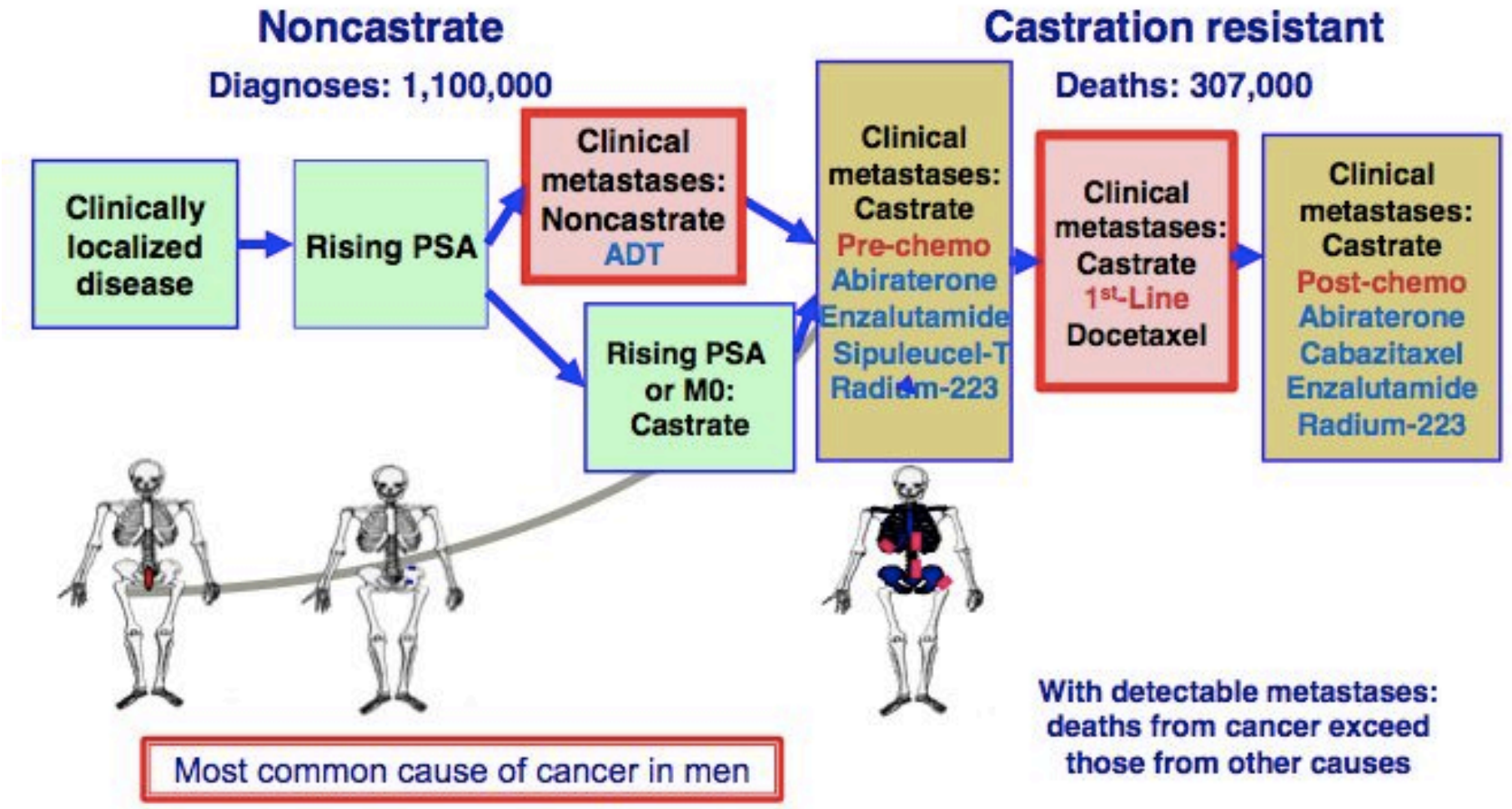
U.O.C. di Oncologia Medica d.U.

Azienda Ospedaliera Universitaria Integrata – Verona

Disclosures

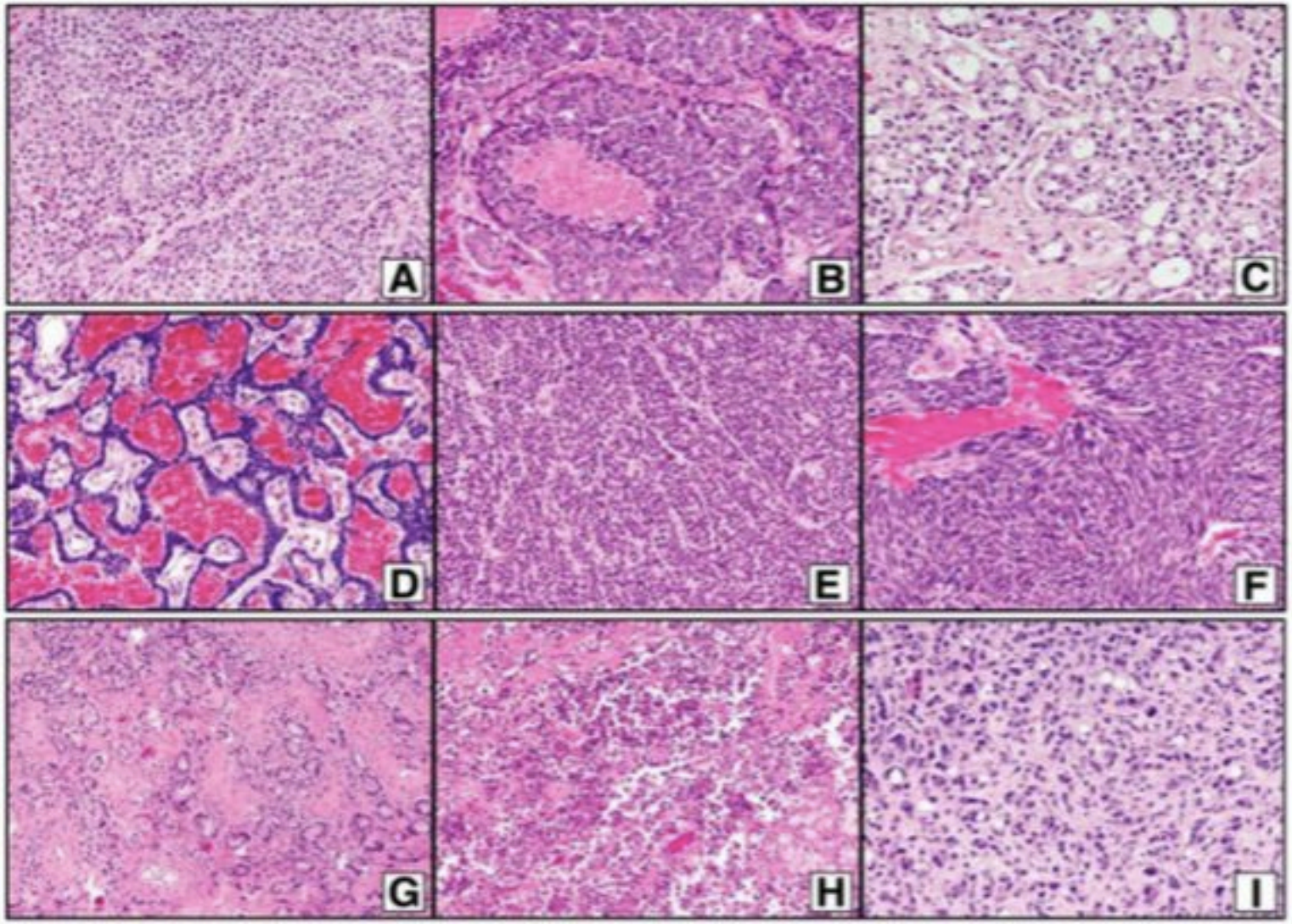
- No pertinent C.O.I. with this presentation
- Advisory Boards/Honoraria/Consultant for:
  - Pfizer
  - Novartis

Prostate cancer is a Continuum of Different Disease Stages



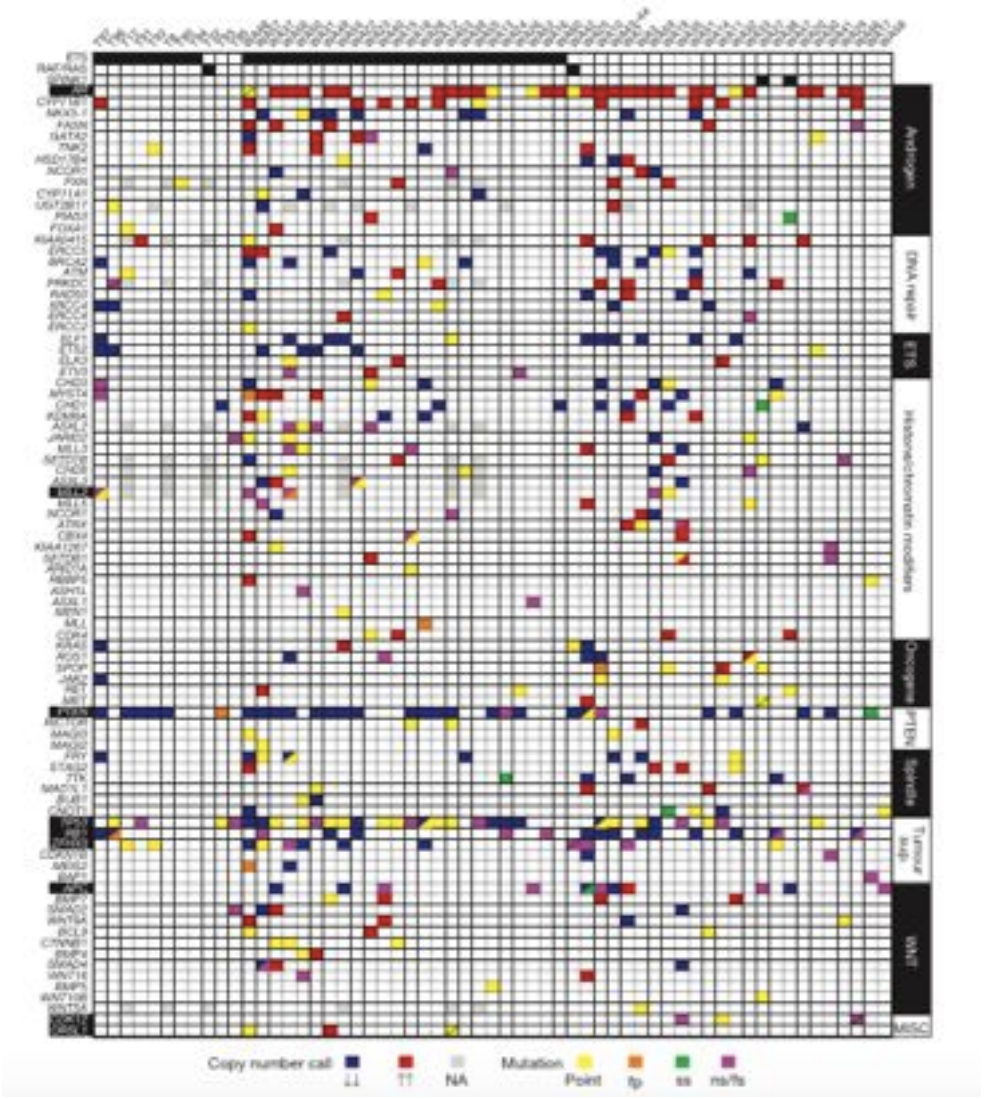
Scher HI. Urology 2000;55:323–7; Jemal A. CA Cancer J Clin 2011;61:69–90
Ferlay A et al. Eur J of Cancer 2013;49:1374– 140
http://globocan.iarc.fr (accessed September 2014)

CRPC is clinically and pathologically heterogeneous



Shah RB et al., Cancer Res 2004 Dec 15; 64 (24): 9209-16

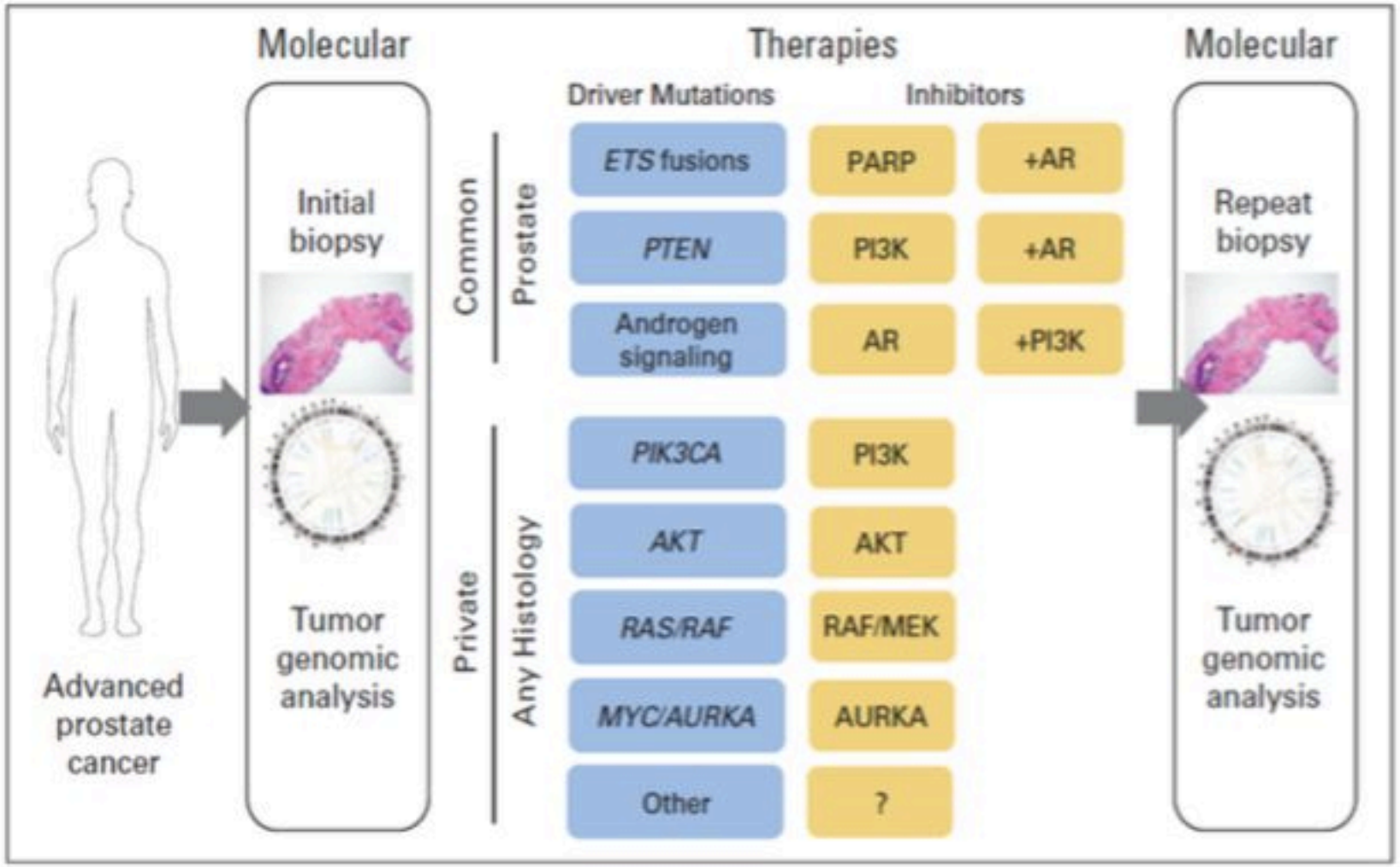
Genomic Complexity in CRPC: May represent a distinct set of druggable targets



- 50 patients: Rapid Autopsy Program
- Prostate Carcinogenesis involves the hijacking/alteration of multiple processes/pathways
- *Next Generation Sequencing*:
  - DNA Repair
  - AR Signaling
  - ETS Gene Rearrangements
  - p53 Mutation
  - PTEN Loss
- 9 genes significantly mutated and 3 others without described roles in prostate cancer

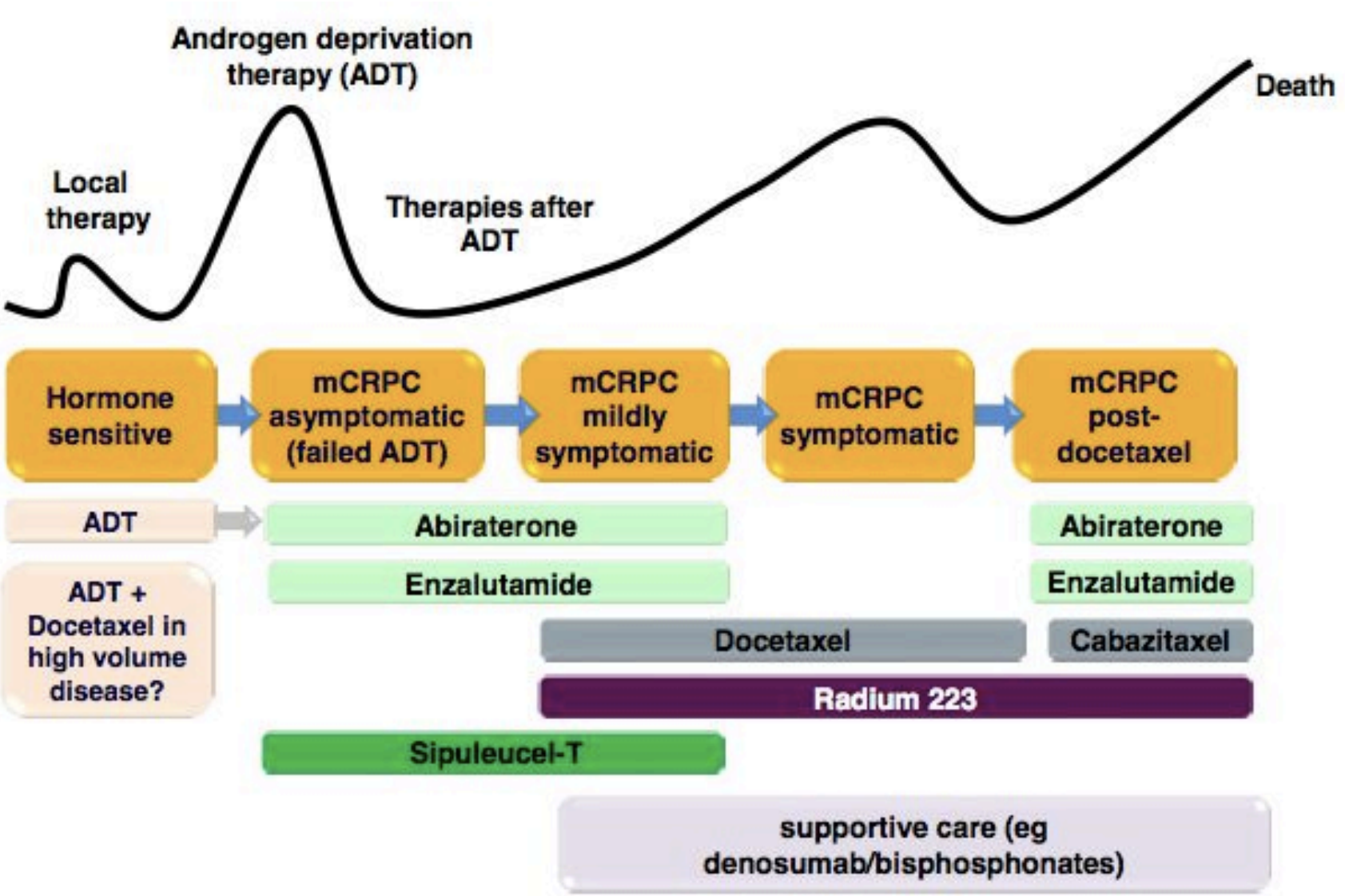
Grasso CS et al., Nature 2012 July 12; 487(7406): 239-43

Advancing Precision Medicine for Prostate Cancer Through Genomics



Roychowdhury S, Chinnaiyan A, J Clin Oncol 2013; 31(15): 1866-73

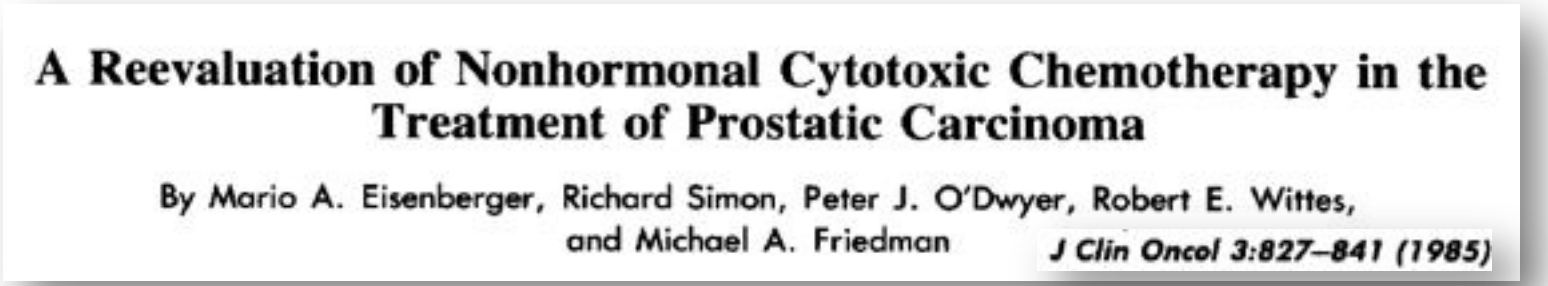
Current Treatment Paradigm is Evolving



Modified by Sternberg CN, Education Prostate – ESMO 2014

Chemotherapy for hormone-resistant prostate cancer

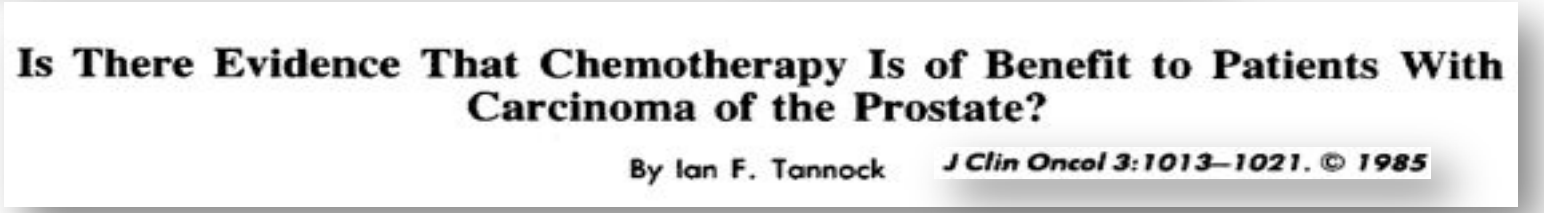
Sporadic small trials were done in the 1980s, and the following reviews were published in 1985.....



A Reevaluation of Nonhormonal Cytotoxic Chemotherapy in the Treatment of Prostatic Carcinoma

By Mario A. Eisenberger, Richard Simon, Peter J. O'Dwyer, Robert E. Wittes, and Michael A. Friedman

J Clin Oncol 3:827–841 (1985)



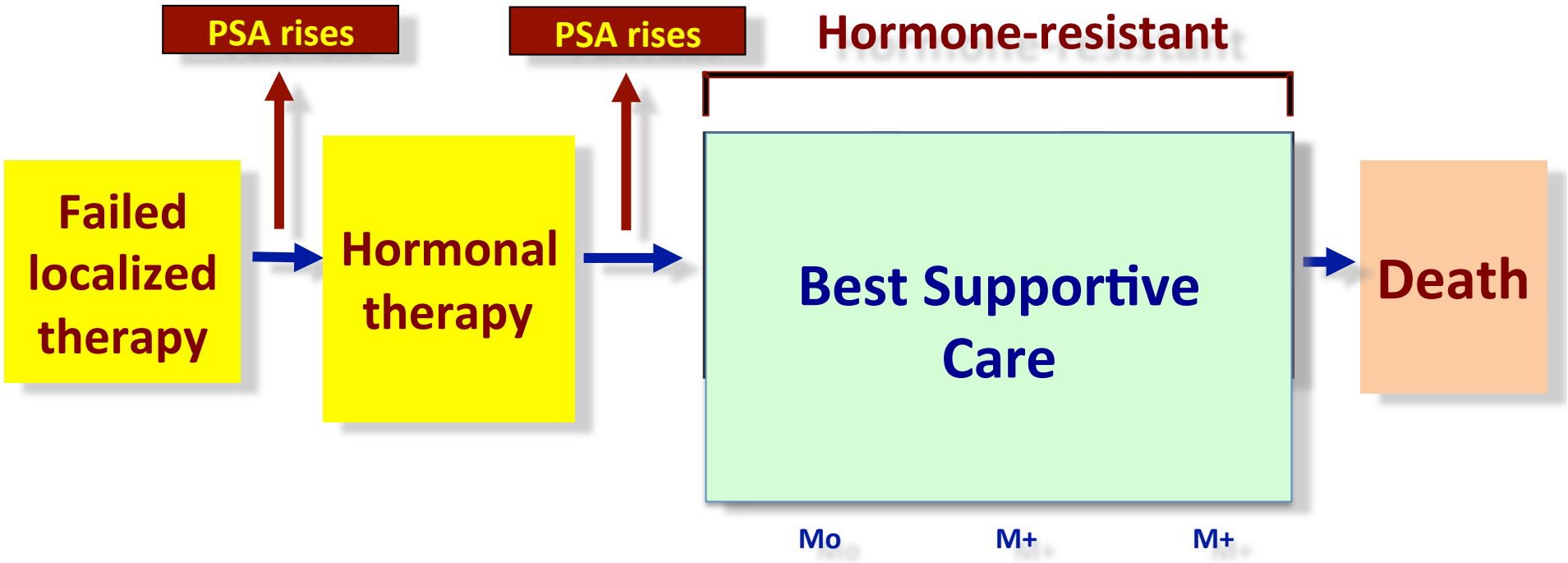
Is There Evidence That Chemotherapy Is of Benefit to Patients With Carcinoma of the Prostate?

By Ian F. Tannock

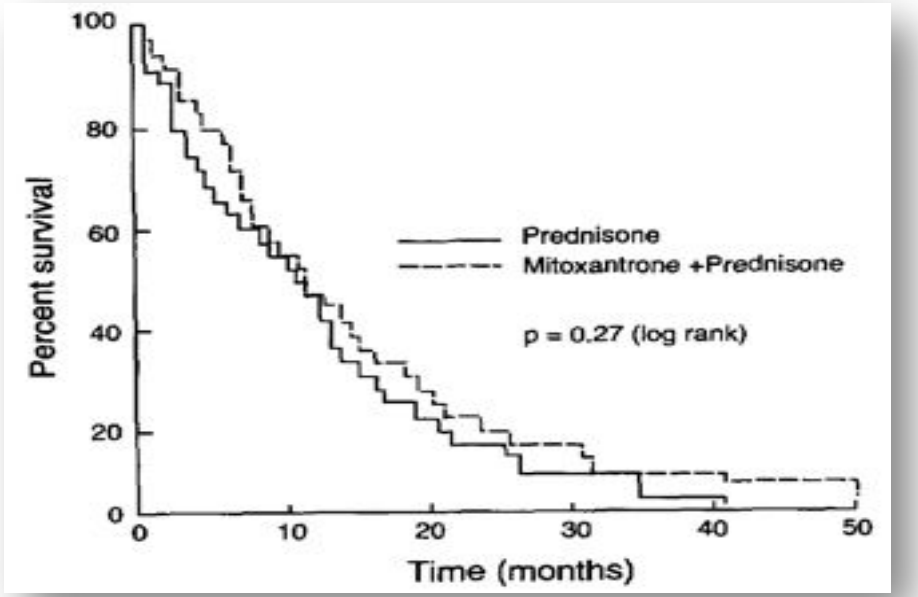
J Clin Oncol 3:1013–1021. © 1985

.....the answer remained: NO

.....until 1996


PSA rises
PSA rises
Hormone-resistant
Failed localized therapy
Hormonal therapy
Best Supportive Care
Death
Mo
M+
M+

MITO plus PDN or PDN alone for symptomatic Hormone-Resistant Prostate Cancer: a Canadian randomized trial with palliative end-points

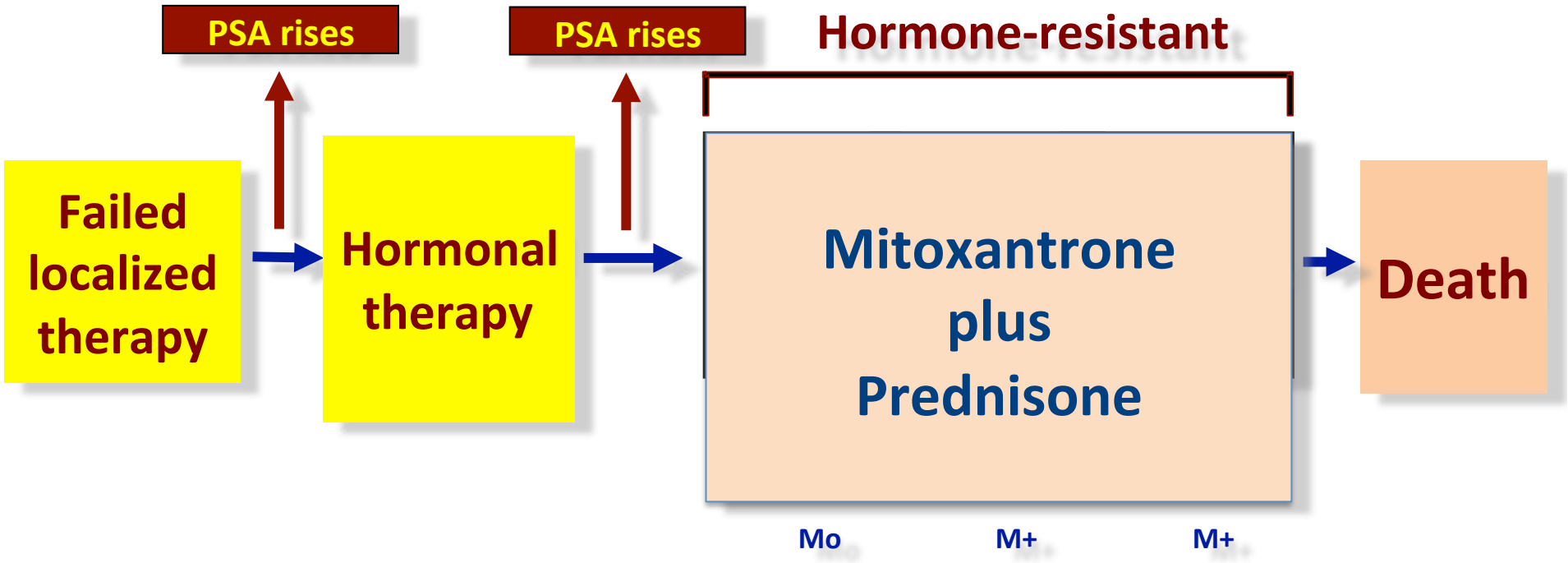


	Prednisone (n=81)	Mitoxantrone & Prednisone (n=80)	*p* Value
Palliative Response	12%	29%	0.01
Duration of Response	18 wks	43 wks	< 0.0001
1° and 2° Palliative Response	21%	38%	0.025
PSA (≥ 50% Decrease)	22%	34%	0.11
Overall Survival	~ 10.3m	~ 10.3m	0.27

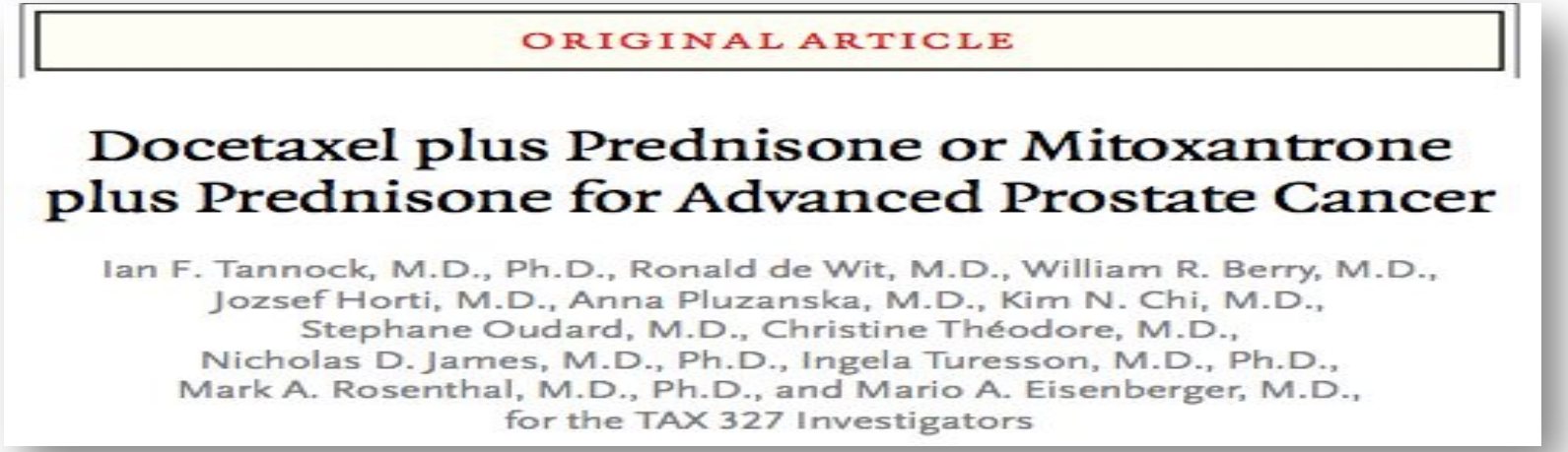
The FDA approved MITO and PDN as palliative treatment for men with symptomatic HRPC – the first time a chemo drug had been approved based on a symptom control endpoint

Tannock IF, JCO 1996

.....until 2004


PSA rises
PSA rises
Hormone-resistant
Failed localized therapy
Hormonal therapy
Mitoxantrone plus Prednisone
Death
Mo
M+
M+

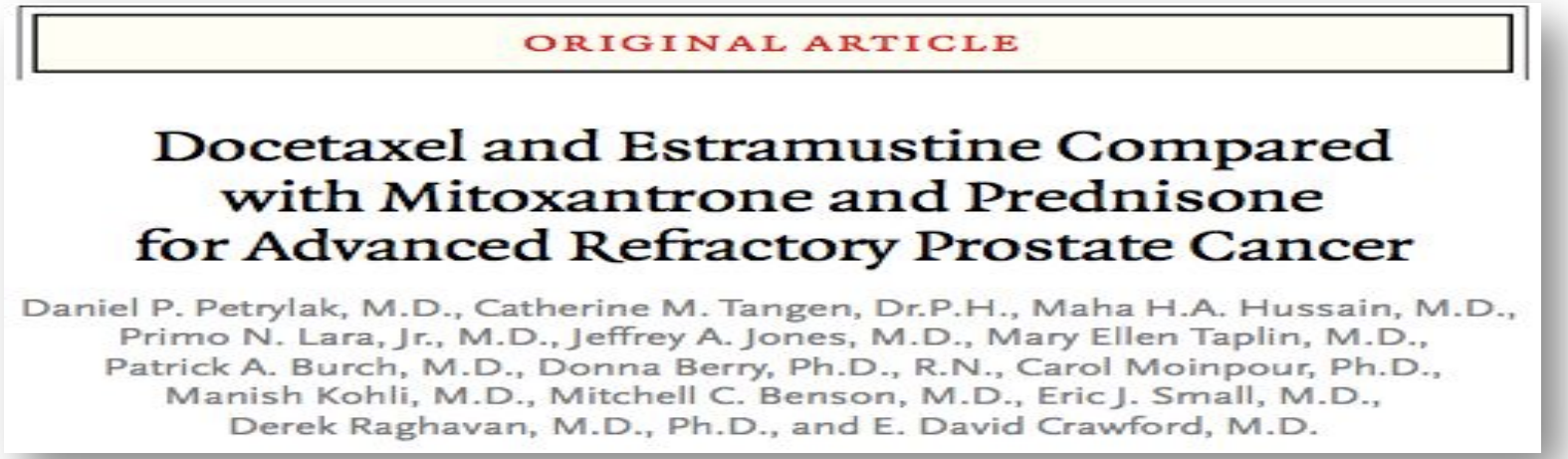
Docetaxel: TAX-327 and SWOG 99-16



ORIGINAL ARTICLE

Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer

Ian F. Tannock, M.D., Ph.D., Ronald de Wit, M.D., William R. Berry, M.D., Jozsef Horti, M.D., Anna Pluzanska, M.D., Kim N. Chi, M.D., Stephane Oudard, M.D., Christine Théodore, M.D., Nicholas D. James, M.D., Ph.D., Ingela Turesson, M.D., Ph.D., Mark A. Rosenthal, M.D., Ph.D., and Mario A. Eisenberger, M.D., for the TAX 327 Investigators

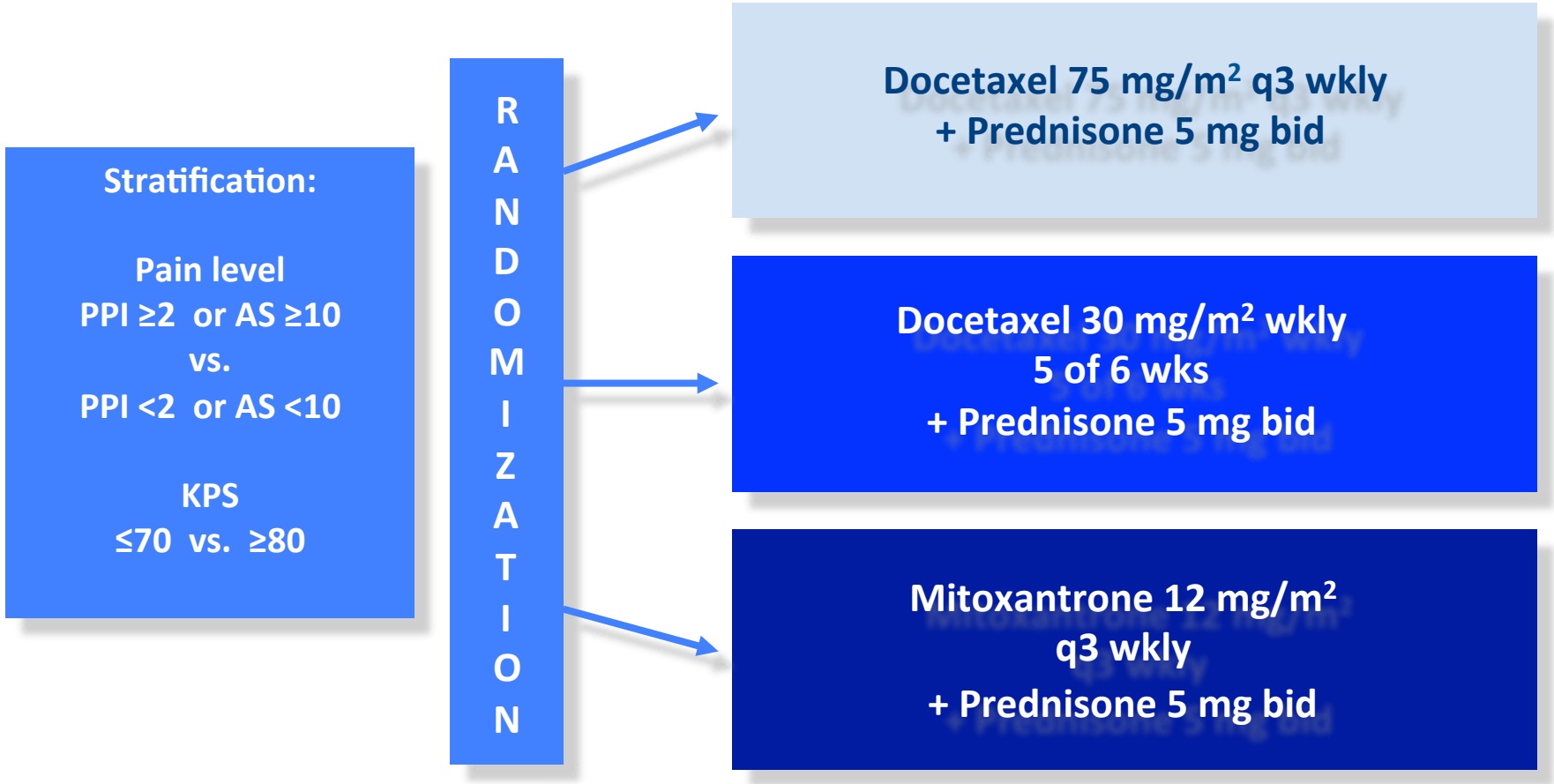


ORIGINAL ARTICLE

Docetaxel and Estramustine Compared with Mitoxantrone and Prednisone for Advanced Refractory Prostate Cancer

Daniel P. Petrylak, M.D., Catherine M. Tangen, Dr.P.H., Maha H.A. Hussain, M.D., Primo N. Lara, Jr., M.D., Jeffrey A. Jones, M.D., Mary Ellen Taplin, M.D., Patrick A. Burch, M.D., Donna Berry, Ph.D., R.N., Carol Moinpour, Ph.D., Manish Kohli, M.D., Mitchell C. Benson, M.D., Eric J. Small, M.D., Derek Raghavan, M.D., Ph.D., and E. David Crawford, M.D.

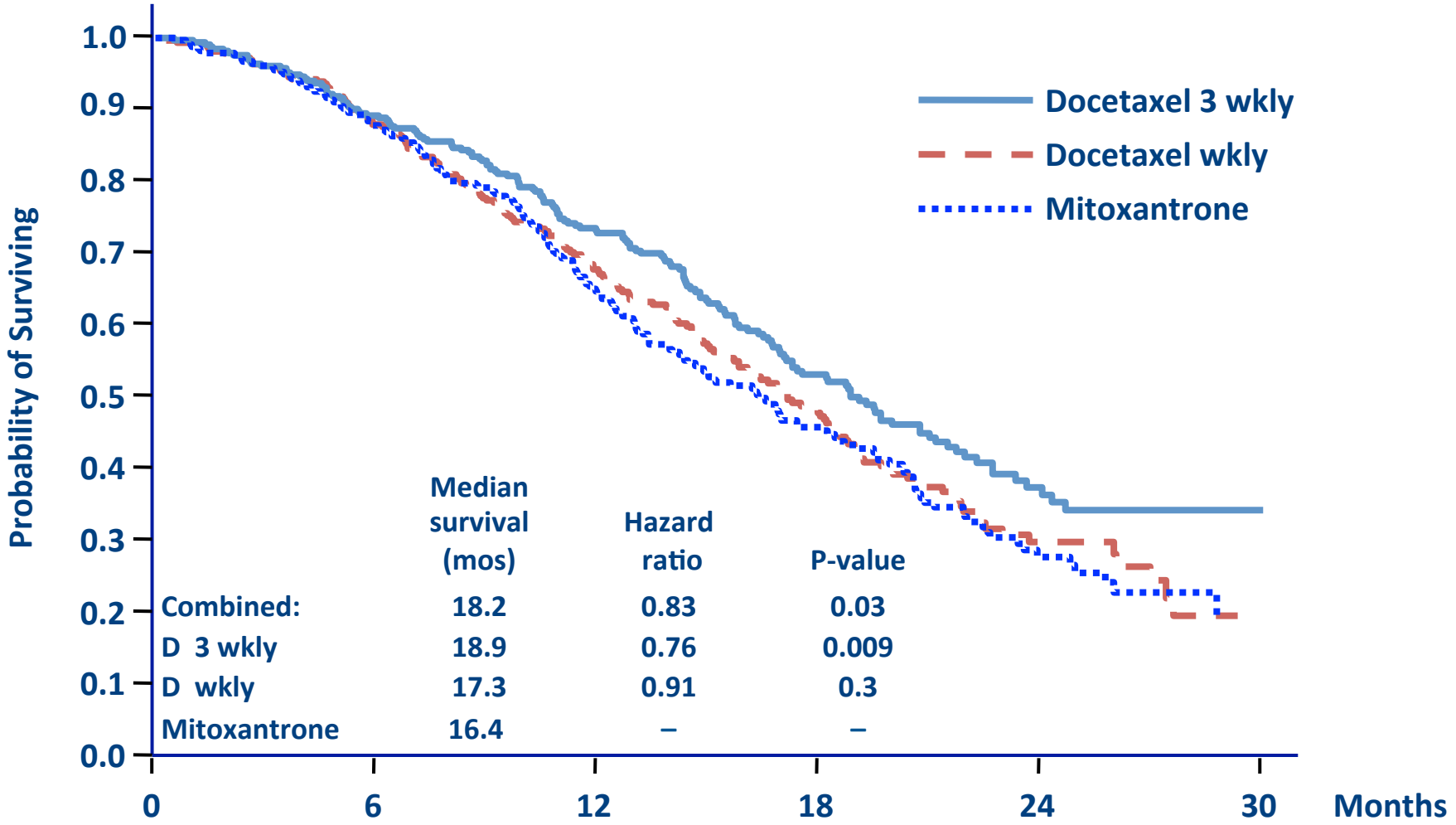
TAX-327 Study: Design



Treatment duration in all 3 arms = 30 wks
***n*=1,006 patients**

Tannock IF, NEJM 2004

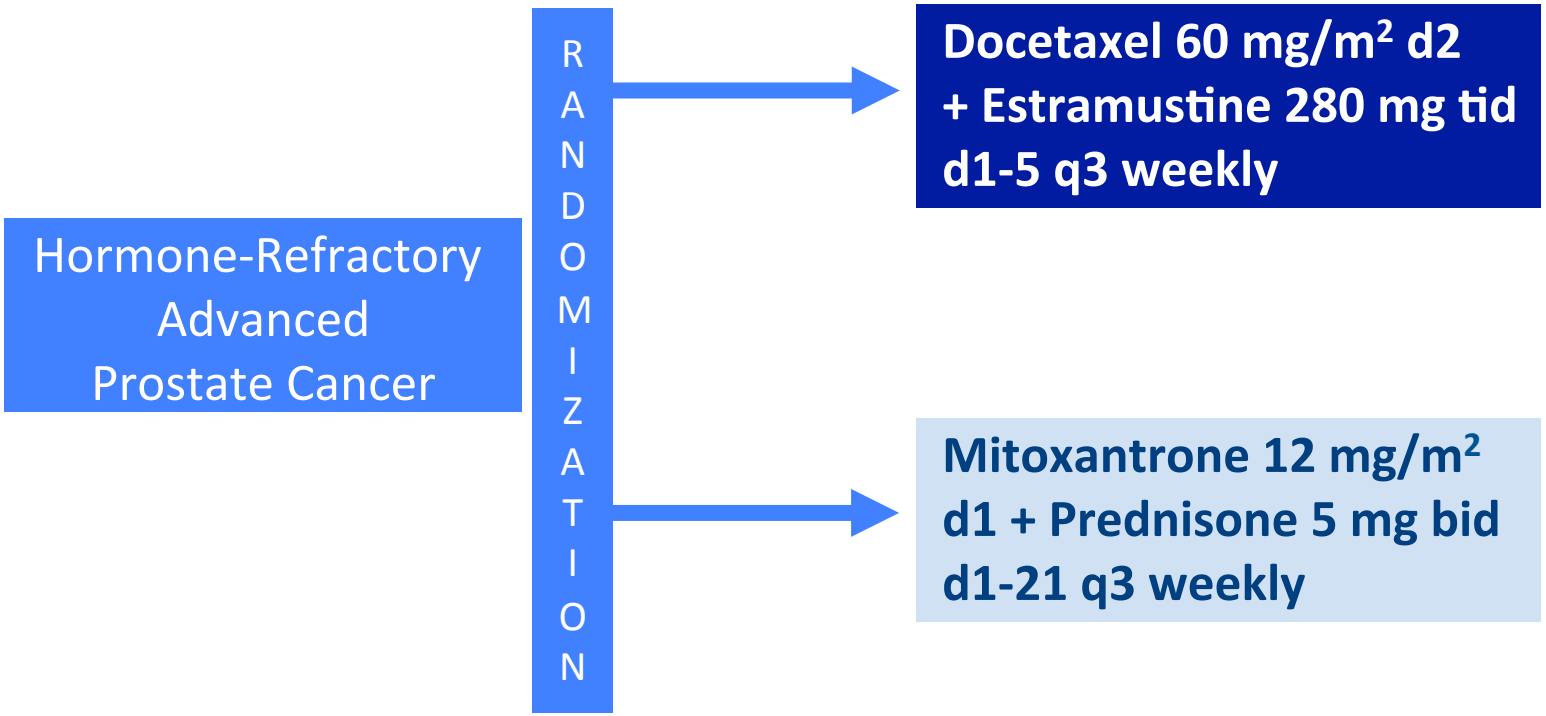
TAX-327: Overall Survival



	Median survival (mos)	Hazard ratio	P-value
Combined:	18.2	0.83	0.03
D 3 wkly	18.9	0.76	0.009
D wkly	17.3	0.91	0.3
Mitoxantrone	16.4	–	–

Tannock IF, NEJM 2004

SWOG 9916: Phase III Trial

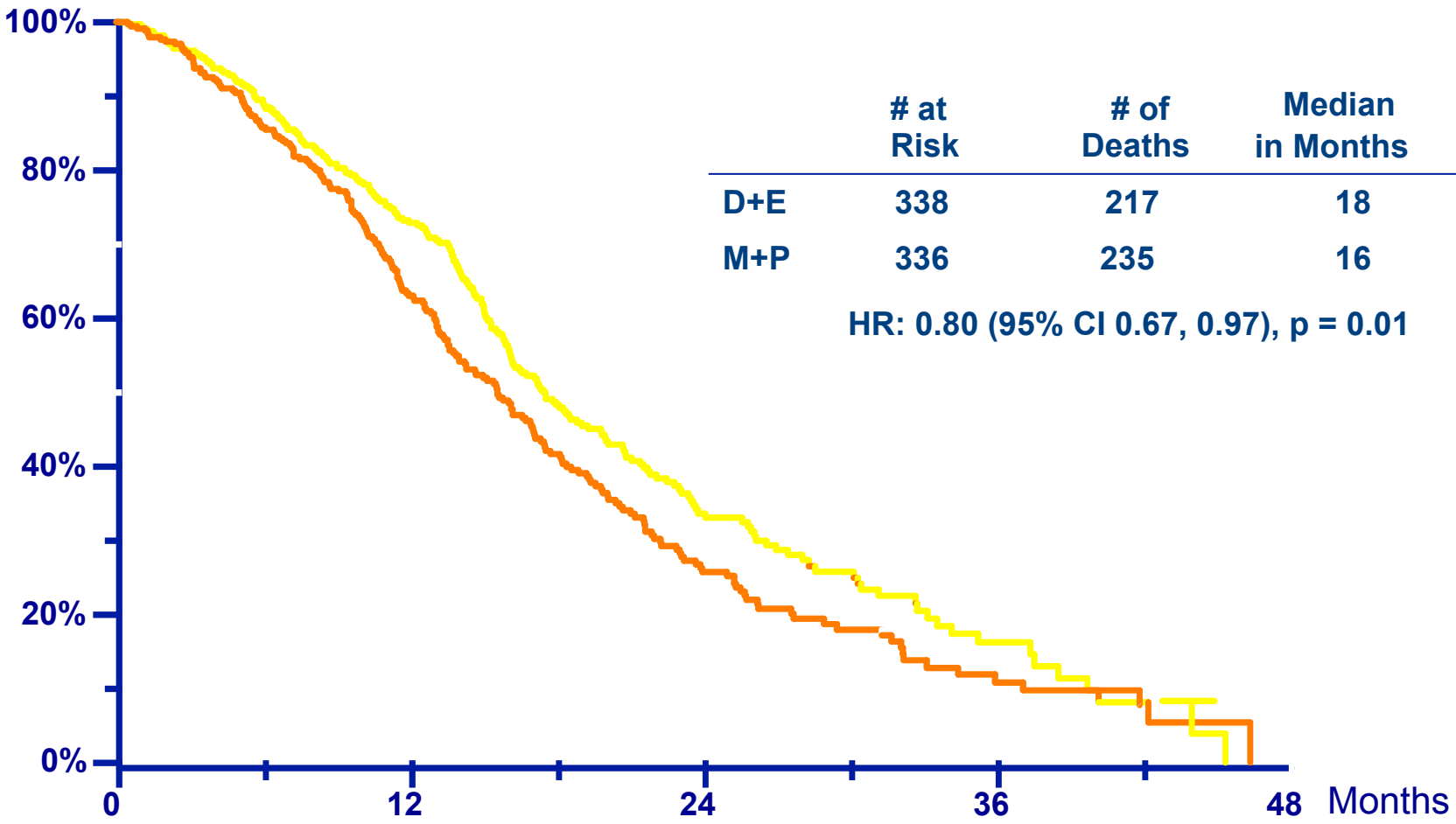


- Survival
- Quality of life:
  - pain questionnaire and log of analgesic requirements
- Improved performance status

n=770 patients

Petrylak DP, NEJM 2004

SWOG 9916: Overall survival



	# at Risk	# of Deaths	Median in Months
D+E	338	217	18
M+P	336	235	16

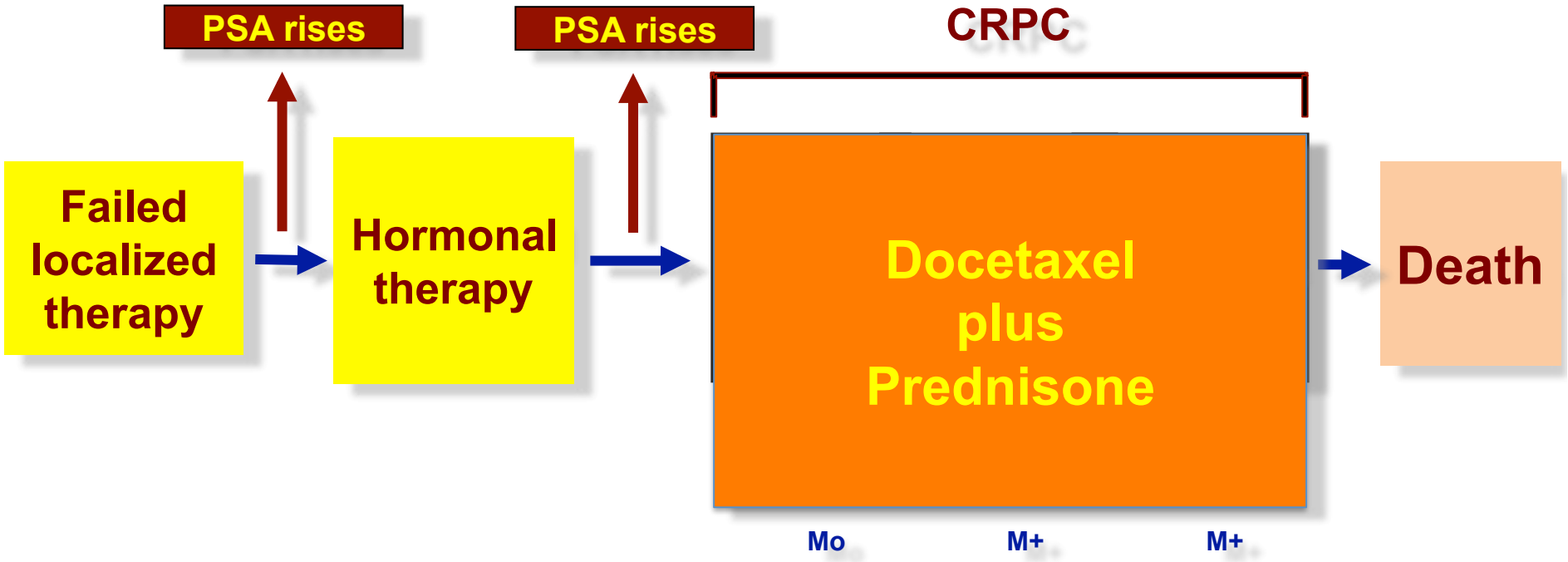
HR: 0.80 (95% CI 0.67, 0.97), p = 0.01

Petrylak DP, NEJM 2004

TAX-327 and SWOG 9916

- Chemotherapy can relieve symptoms and improve QoL
- Estramustine adds only toxicity and should not be used
- Docetaxel chemotherapy given every three weeks increases overall survival
  - decrease risk of death by 24%
  - absolute increase in median survival of 2.5 months
- Docetaxel chemotherapy demonstrates a higher rate of pain response, quality of life improvement and PSA
- On the basis of survival advantage, ***docetaxel + prednisone is the preferred treatment for most patients with mCRPC***

.....until 2013


PSA rises
PSA rises
CRPC
Failed localized therapy
Hormonal therapy
Docetaxel plus Prednisone
Death
Mo
M+
M+

Combining drug X to docetaxel: a failing strategy so far…

- Doc + Oblimersen
- Doc + DN-101
- Doc + Bevacizumab
- Doc + VEGF-Trap
- Doc + Lenalidomide
- Doc + Atrasentan
- Doc + Zibotentan
- Doc + Dasatinib

Negative Phase III trials

Courtesy of K. Fizazi

Phase II clinical trials of docetaxel-based combination therapy for mCRPC (1)

Author	Combination Agent	n	>50% PSA decline, n/N (%)	Tumor response, n/N (%)	Median Survival
Salzberg M et al.	**Gefitinib**	37	17/37 (45)	9/37 (24) PR	447 days (14.7 months)
Gross M et al.	**Erlotinib**	22	5/22 (23)	0/22 (0)	24.6 months
Horti J et al.	**Vandetanib (+ prednisone daily)**	43	17/43 (40)	3/38 (8) PR	Not reported
Mathew P et al.	**Imatinib**	116	11/40 (28)	2/24 (8)[a]	20.9 months
Cetnar JP et al.	**Sorafenib**	13	6/13 (46)	Not reported	Not reported
Zurita AJ et al.	**Sunitinib (+ prednisone daily)**	55	31/55 (56)	13/33 (39) confirmed PR; 7/33 (21) unconfirmed PR	Not reached
Araujo J et al.	**Dasatinib (+ prednisone daily)**	46	21/43 (49)	13/31 (42) confirmed PR; 3/31 (10) unconfirmed PR	Not reported
Picus J et al.	**Bevacizumab + estramustine**	79	13/20 (65)	17/32 (53) PR	Not reported
Di Lorenzo G et al.	**Bevacizumab**	20	11/20 (55)	3/8 (38) PR	9 months
Ning YM et al.	**Bevacizumab + thalidomide (+ prednisone daily)**	60	51/58 (88)	2/32 (6) CR; 18/32 (56) PR	Not reported
Dahut WL et al.	**Thalidomide**	50	25/47 (53)	7/20 (35) PR[a]	28.9 months
Pili R et al.	**Vadimezan**	38	6/26 (23)	Not reported	Not reported
Armstrong AJ et al.	**Atrasentan**	31	7/31 (23)	2/13 (15) PR	17.6 months

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Phase II clinical trials of docetaxel-based combination therapy for mCRPC (2)

Author	Combination Agent	n	>50% PSA decline, n/N (%)	Tumor response, n/N (%)	Median Survival
Morris MJ et al.	**Samarium 153**	52	22/50 (44)	Not reported	Not reported
Fizazi K et al.	**Samarium 153 (consolidation)**	43	33/43 (77)	Not reported	29 months
Tolcher AW et al.	**Oblimersen**	28	14/27 (52)	4/12 (33)[a]	19.8 months
Sternberg CN et al.	**Oblimersen**	54	20/54 (37)	5/21 (37) PR	Not reported
MacVicar GR et al.	**AT-101 (+ prednisone daily)**	36	24/36 (67)	8/19 (42) confirmed PR; 1/19 (5) unconfirmed PR	Not reported
Poiesz B et al.	**AT-101**	40	6/34 (18)	3/21 (14) confirmed PR o CR; 2/21 (10) unconfirmed PR	Not reported
Small E et al.	**GVAX**	204	Not reported	Not reported	12.2 months
Beer TM et al.	**DN-101**	125	79/125 (63)	14/48 (29)	24.5 months
Carles J et al.	**Celecoxib (+ estramustine)**	48	28/48 (58)	4/19 (21) confirmed CR or PR	19.2 months
Dreicer R et al.	**Bortezomib**	83	19/67 (28)	3/45 (7) confirmed PR 2/45 (4) unconfirmed PR	Not reported
Hainsworth JD et al.	**Bortezomib**	63	15/60 (25)	Not reported	13.8 months
Dawson NA et al.	**Exisulind**	80	(47/75 (63)	6/46 (13) PR	17.8 months
Chi KN et al.	**OGX-011 (+ prednisone daily)**	41	23/40 (53)	5/26 (19) PR	23.8 months

[a]Tumor response according to non-RECIST criteria.

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Phase III trials of first-line docetaxel-based combination therapy in mCRPC

Author	Trial	Treament	n	Primary Endpoint	Secondary Endpoints
Tannock IF et al.	VENICE	**Aflibercept** + docetaxel vs Placebo + docetaxel (plus prednisone)	1224	OS (22.1 vs 21.2 months; *P*.38)	PFS (6.9 vs 6.2 months; *P*.31) PSA-PFS (8.3 vs 8.1 months; *P*.42) SREs (15.3 vs 15.0 months; *P*.31) Pain-PFS (9.2 vs 9.7 months; *P*.87) PSA-response (68.6 vs 63.5%)
Kelly WK et al.	CALGB-90401	**Bevacizumab** + docetaxel Vs Placebo + docetaxel (plus prednisone)	1050	OS (22.6 vs 21.5 months; *P*.181)	**PFS (9.9 vs 7.5 months; *P*<.001)** **ORR (49.4% vs 35.5%; *P*.0013)** **PSA-decline (69.5% vs 57.9%; *P*.001)**
Quinn DI et al.	SWOG S0421	**Atrasentan** + docetaxel vs Placebo + docetaxel (plus prednisone)	994	OS (17.8 vs 17.6 months; *P*.64) PFS (9.2 vs 9.1 months; *P*.81)	RECIST confirmed response (14 vs 14%; *P*.97) PSA-decline (50 vs 49%; *P*.75) Grade 4+ toxicity (57 vs 60%; *P*.22)
Fizazi K et al.	ENTHUSEM1C	**Zibotentan** + docetaxel vs Placebo + docetaxel (plus prednisone)	1052	OS (HR 1.00; 95% CI 0.84-1.18; *P*.963)	TTPP (9.3 vs 10 months) TTPR (HR 0.84; 95% CI 0.61-1.16; *P*.283) PSA-RR (53.2 vs 56.4%)
Araujo JC et al.	READY	**Dasatinib** + docetaxel vs Docetaxel + placebo (plus prednisone)	1522	OS (21.2 vs 21.5 months; *P*.9009)	PFS (11.1 vs 11.8 months; *P*.21) PSA progression (7.6 vs 8.0 months; *P*.14) ORR (31.9 vs 30.5%; *P*.67) SERs (31.1 months vs not reached; *P*.076)
Petrylak DP et al.	MAINSAIL	**Lenalidomide** + docetaxel vs Placebo + docetaxel (plus prednisone)	1059	OS (77 weeks vs not reached; *P*.0017)	PFS (45 vs 46 weeks; *P*.0187) ORR (22.1 vs 24.3%; *P*.39) PSA response (58.7 vs 57.0%)
Scher et al.	ASCENT2	**DN101** + docetaxel vs Docetaxel (plus prednisone)	953	OS (17.8 vs 20.2 months; *P*.002)	NR
NR	VITAL2[a]	**GVAX vaccine** + docetaxel vs Docetaxel (plus prednisone)	NR	OS	TTP TTPP
Chi KN et al	SYNERGY	Docetxel +/- **Custirsen** (OGX-011)	1022	OS	PFS, PSA, patient reported outcomes, serum clusterin, safety
Pirrie S et al.	TRAPEZE	Docetaxel/pdn +/- **Strontium** or Zoledronate or both	NR	Bony clinical PFS composite	OS SREs

[a]Stopped trial.

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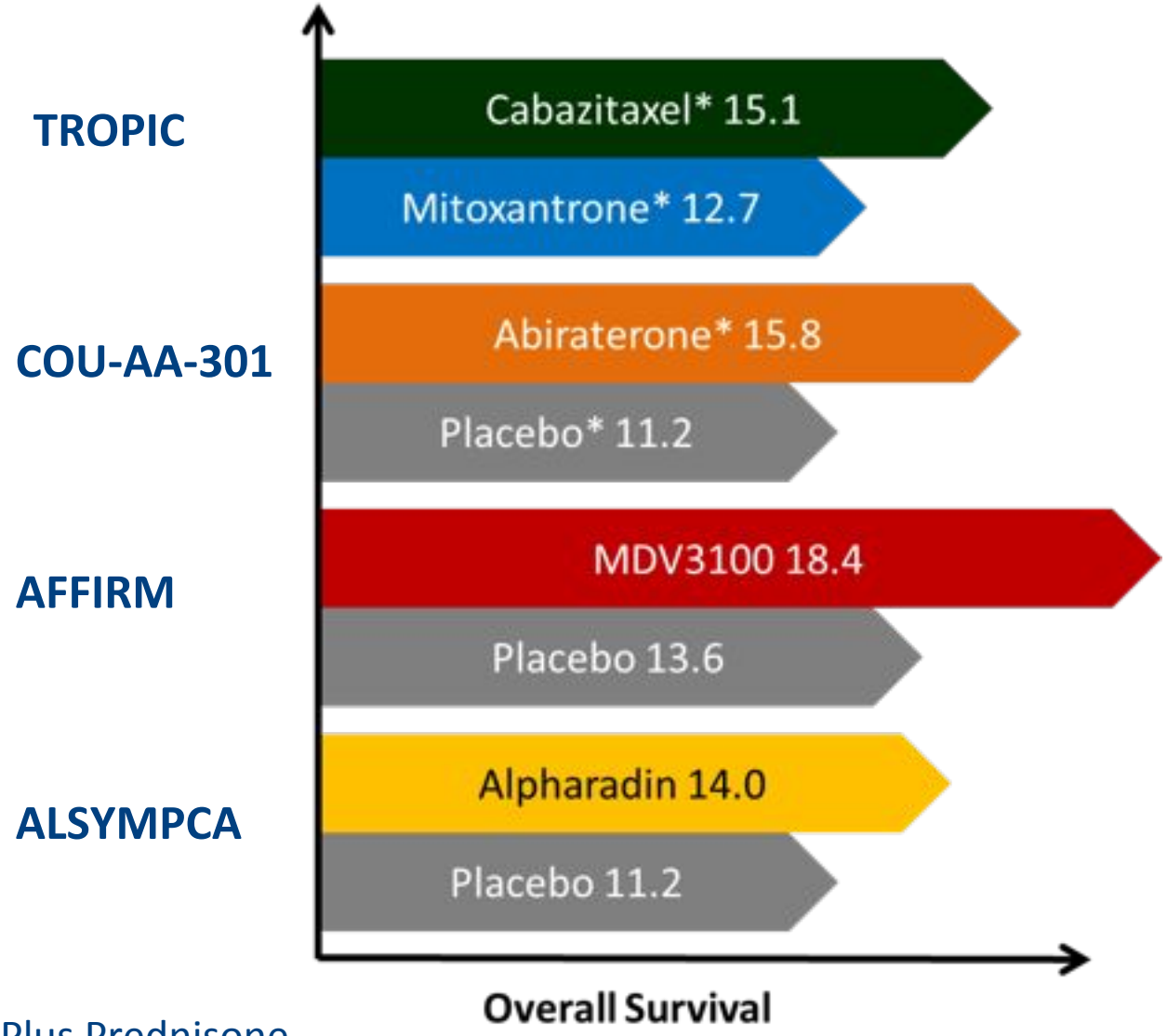
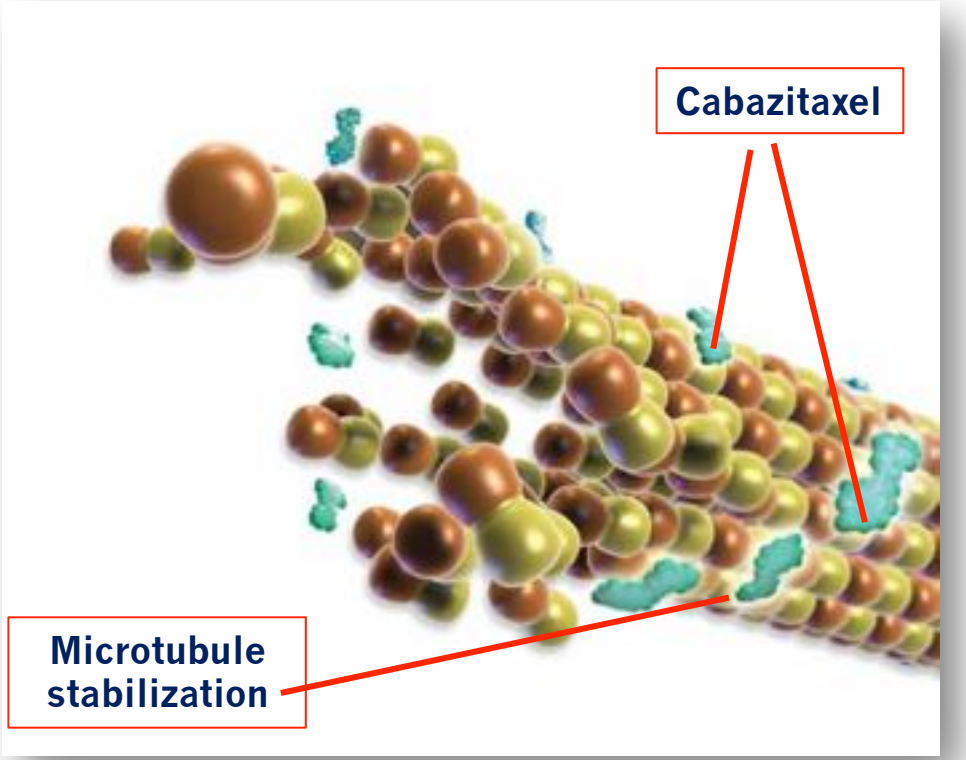
Second line therapy: different options



* Plus Prednisone

Cabazitaxel

- Selected over 450 docetaxel analogues for its ability to overcome taxane resistance
- As potent as docetaxel against sensitive cell lines and tumor models
- Active in vitro and in vivo against tumor models resistant to currently available taxanes



Cabazitaxel Preclinical Summary

	Docetaxel	Cabazitaxel
Stabilization of microtubules	√	√
Activity in taxane-sensitive cell lines	√	√
Activity in taxane-sensitive in vivo tumor models	√	√
Orally bioavailable in murine models		√
Active in chemotherapy-resistant or insensitive cell lines		√
Active in chemotherapy-resistant or insensitive *in vivo* tumor models		√
Crosses blood-brain-barrier *in vivo*		√

Cabazitaxel Preclinical Summary

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Activity in taxane-sensitive in vivo tumor models	√	√
Orally bioavailable in murine models		√
Active in chemotherapy-resistant or insensitive cell lines		√
Active in chemotherapy-resistant or insensitive *in vivo* tumor models		√
Crosses blood-brain-barrier *in vivo*		√

Phase III TROPIC trial

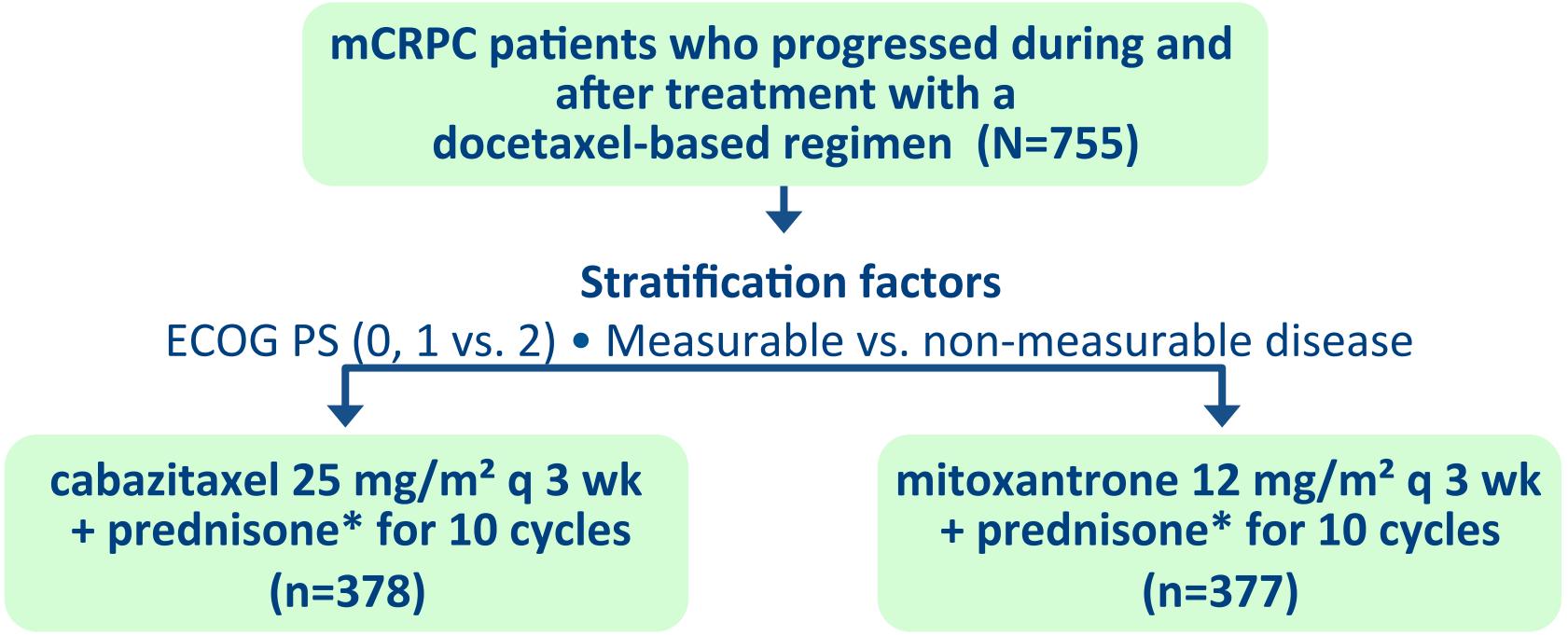
Cabazitaxel + prednisone (CBZP) versus mitoxantrone + prednisone (MP) in the treatment of metastatic castration-resistant prostate cancer (mCRPC) previously treated with a docetaxel-based regimen

O. Sartor, S. Oudard, M. Ozguroglu, S. Hansen, J. P. H. Machiels, L. Shen, S. Gupta, J. S. De Bono,
for the TROPIC Investigators


Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial

Johann Sebastian de Bono, Stephane Oudard, Mustafa Ozguroglu, Steinbjørn Hansen, Jean-Pascal Machiels, Ivo Kocak, Gwenaëlle Gravis, Istvan Bodrogi, Mary J Mackenzie, Liji Shen, Martin Roessner, Sunil Gupta, A Oliver Sartor, for the TROPIC Investigators

Phase III TROPIC trial

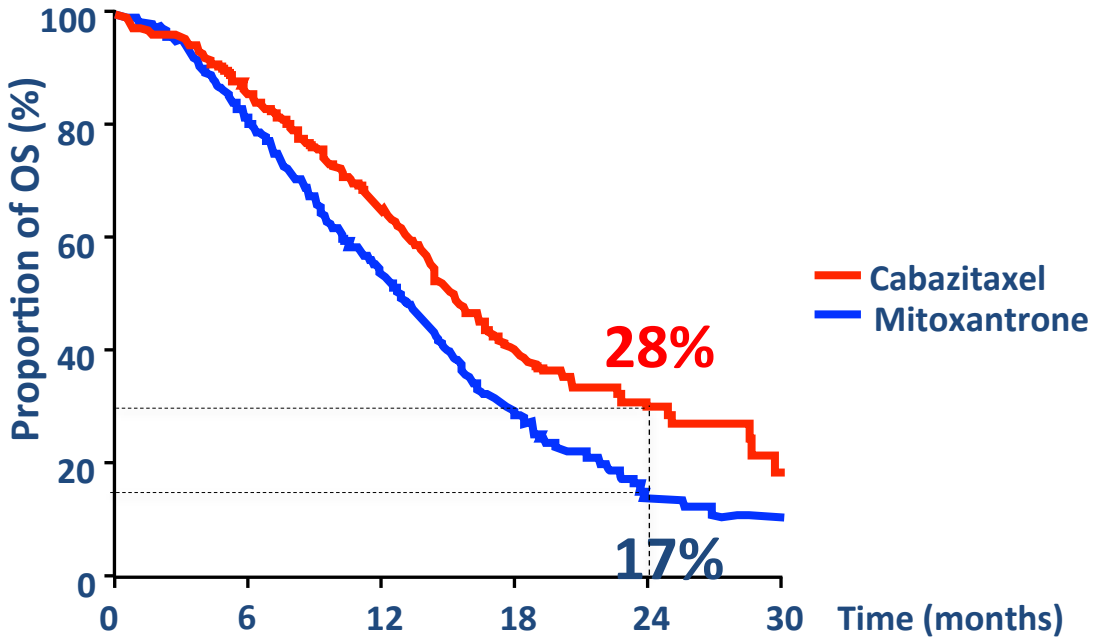


*Oral prednisone/prednisolone: 10 mg daily

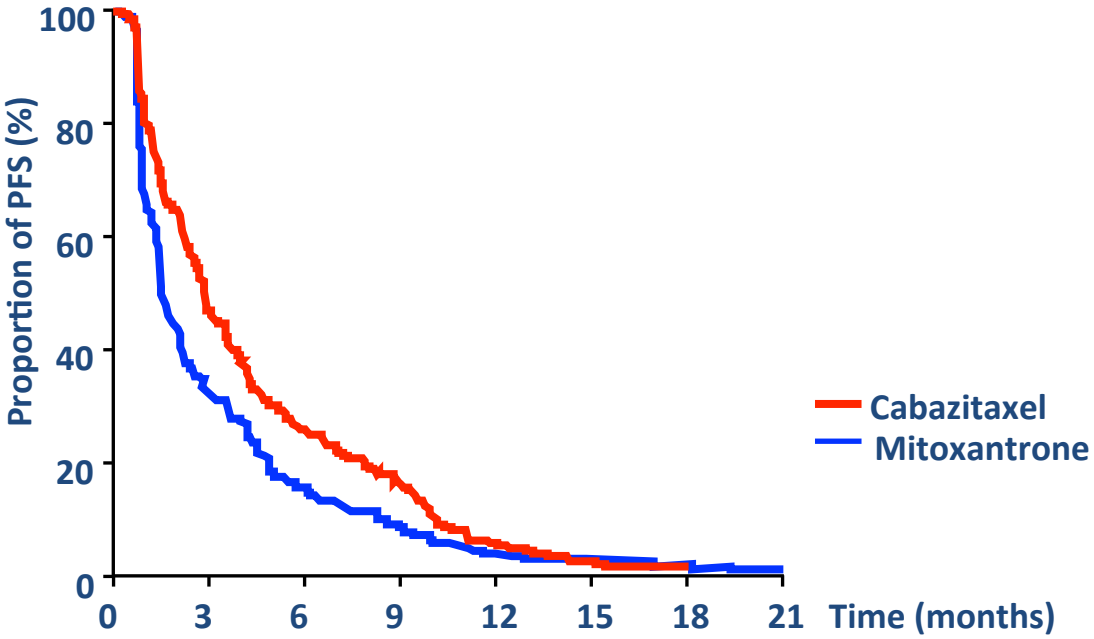
Primary endpoint: OS

Secondary endpoints: Progression-free survival (PFS), response rate, and safety

Inclusion: Patients with measurable disease must have progressed by RECIST; otherwise must have had new lesions or PSA progression



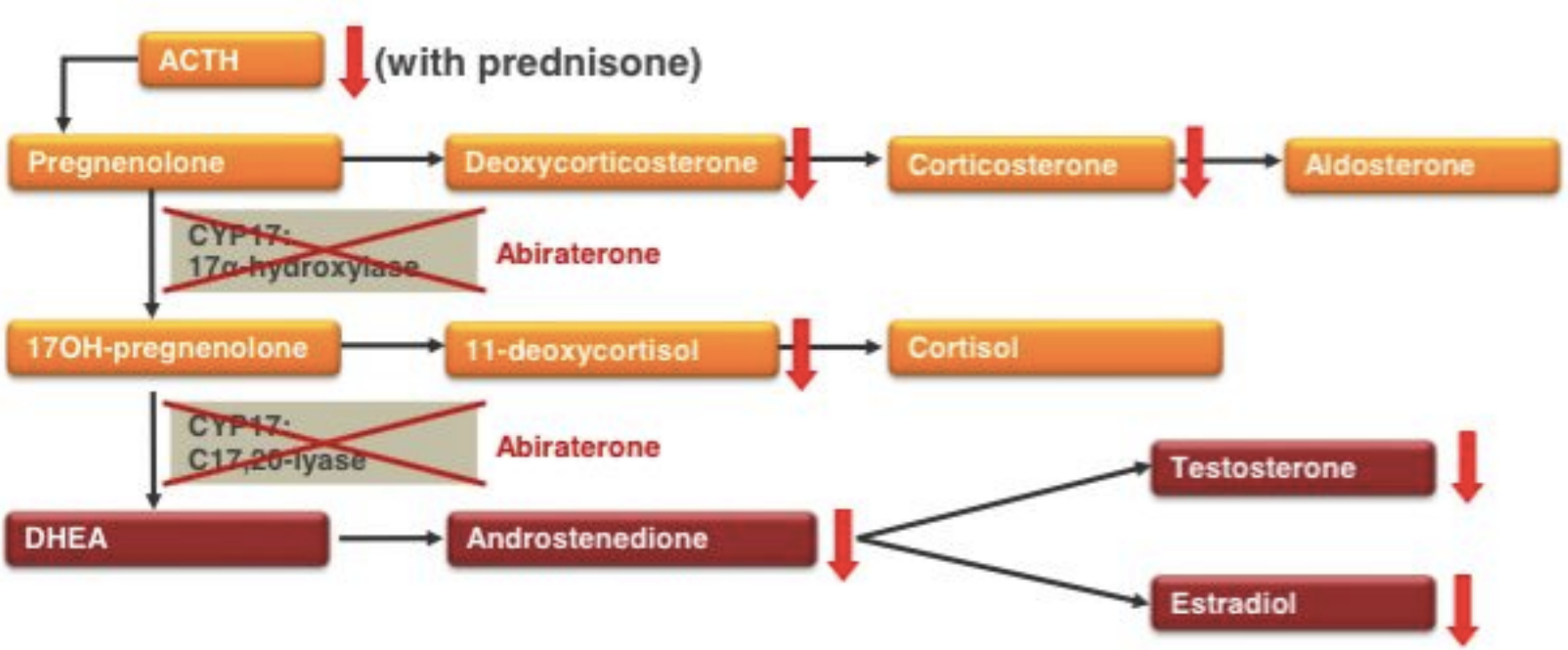
	MP	CBZP
Median OS (months)	12.7	15.1
Hazard ratio	0.70	
95% CI	0.59–0.83	
P value	<0.0001	



	MP	CBZP
Median PFS (months)	1.4	2.8
Hazard ratio	0.74	
95% CI	0.64–0.86	
P-value	<0.0001	

De Bono et al. *Lancet*, 2010, 376:1147-54

Abiraterone inhibits CYP17: 17α-hydroxylase/17,20-lyase

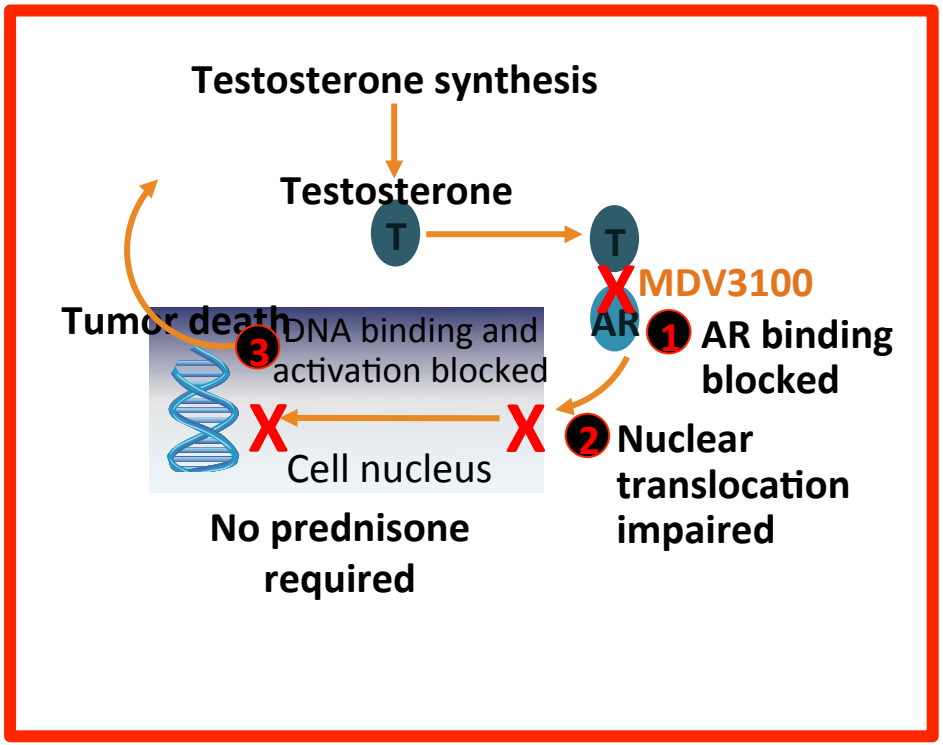


Attard G et al, J Clin Oncol 2008; 26:4563-71

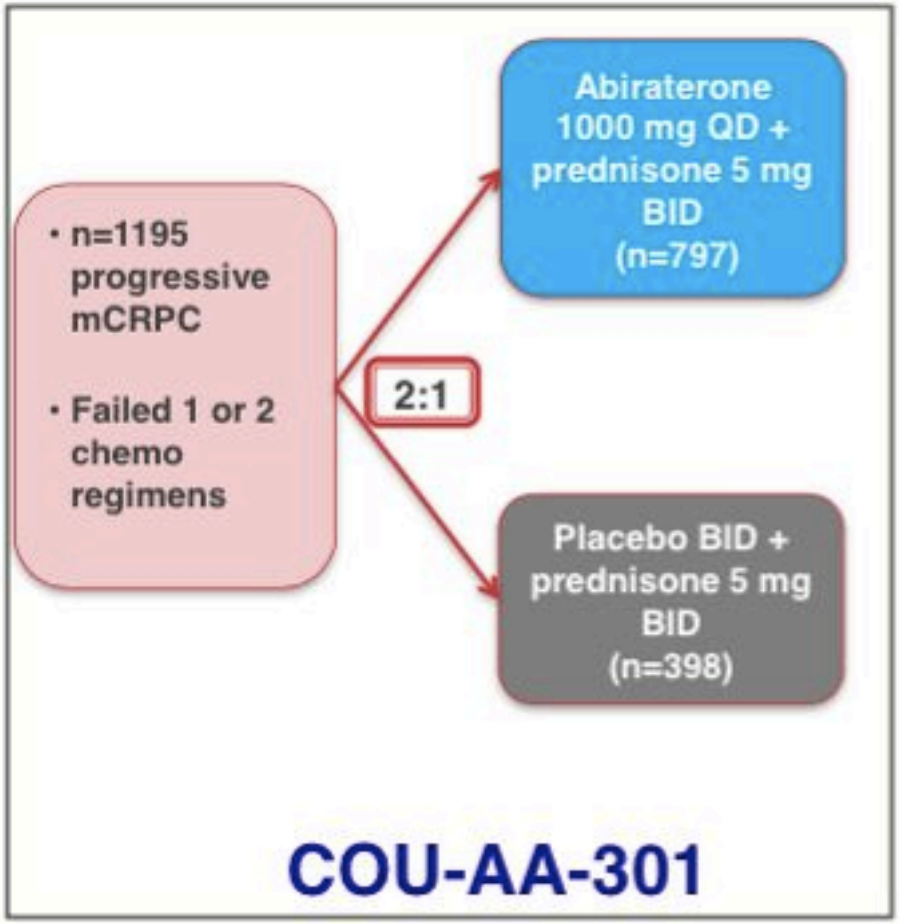
MDV3100: ENZALUTAMIDE

Antiandrogen with three effects on Androgen Receptor:

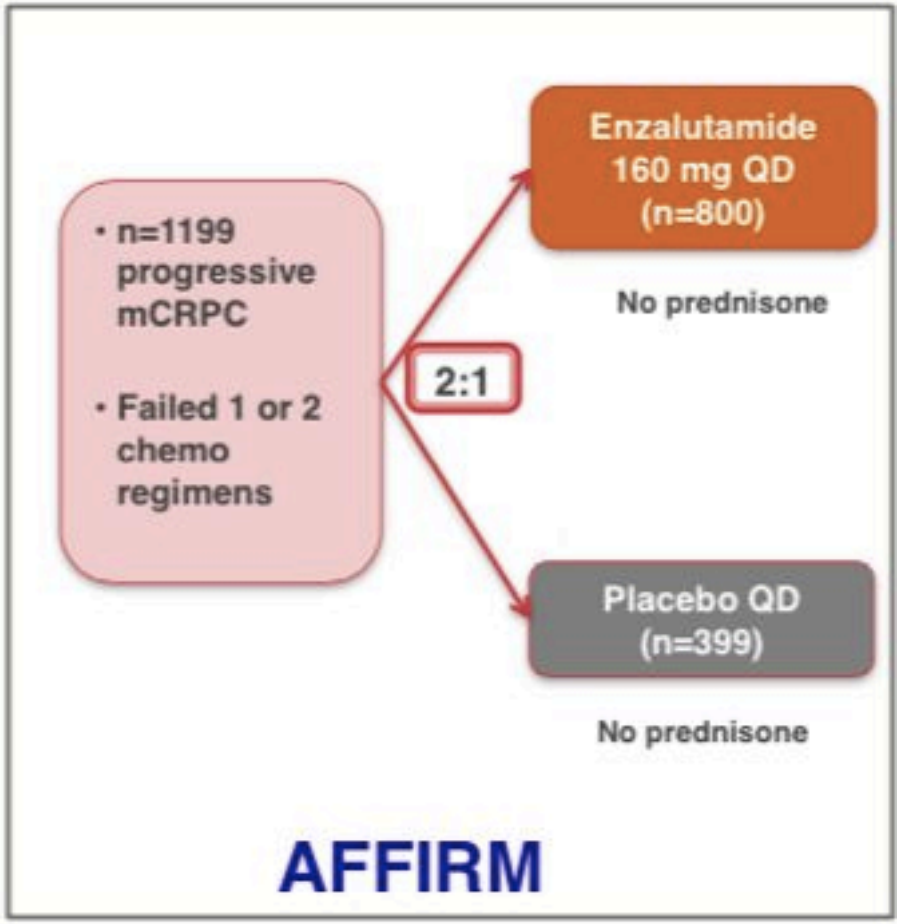
- AR inhibition
- AR degradation
- Inhibition of AR transport into prostate cancer cell nucleus



Abiraterone and Enzalutamide in mCRPC
Phase III Study Post-Docetaxel
Primary end point: OS

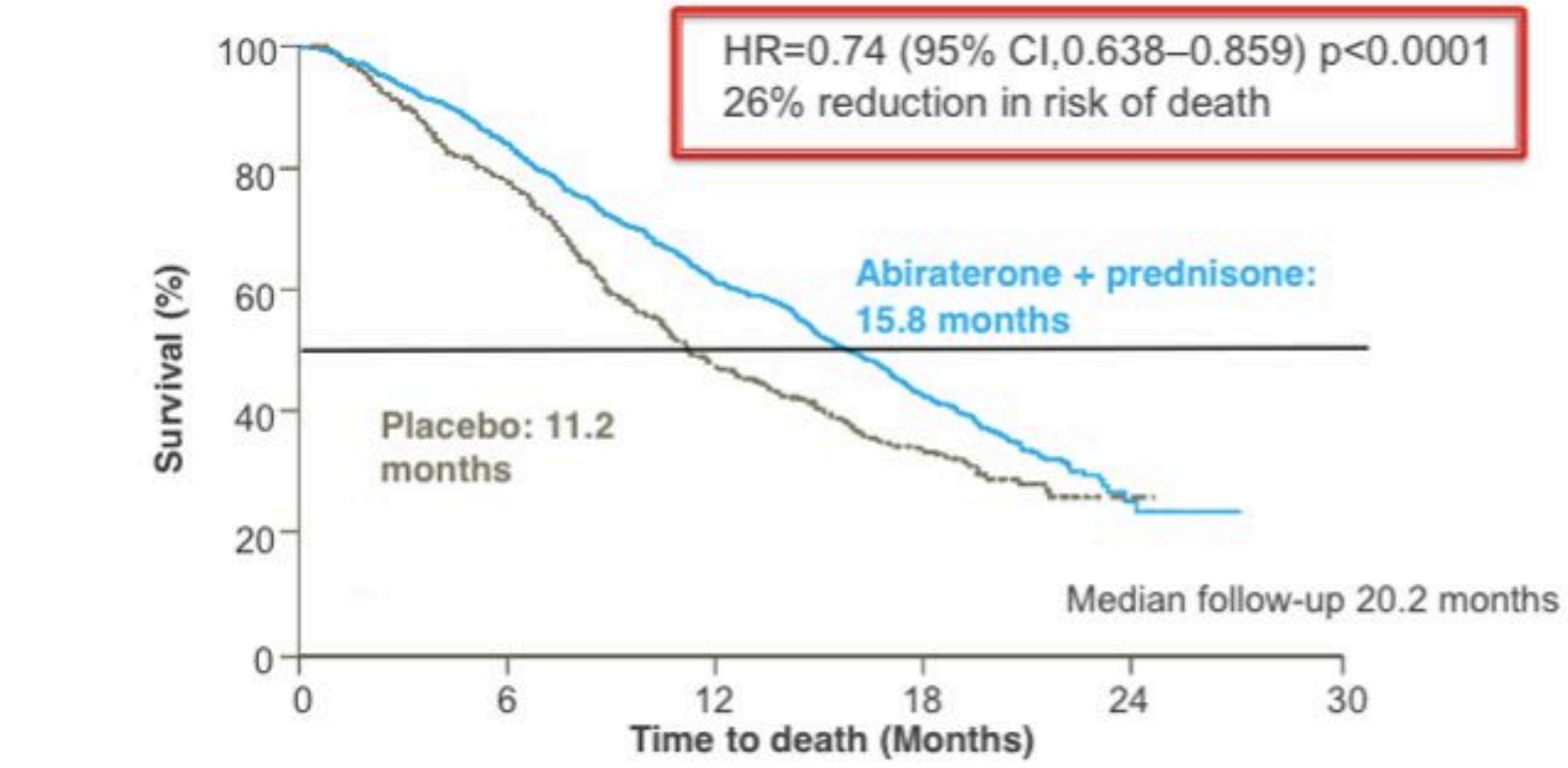


de Bono JS, et al. NEJM 2011



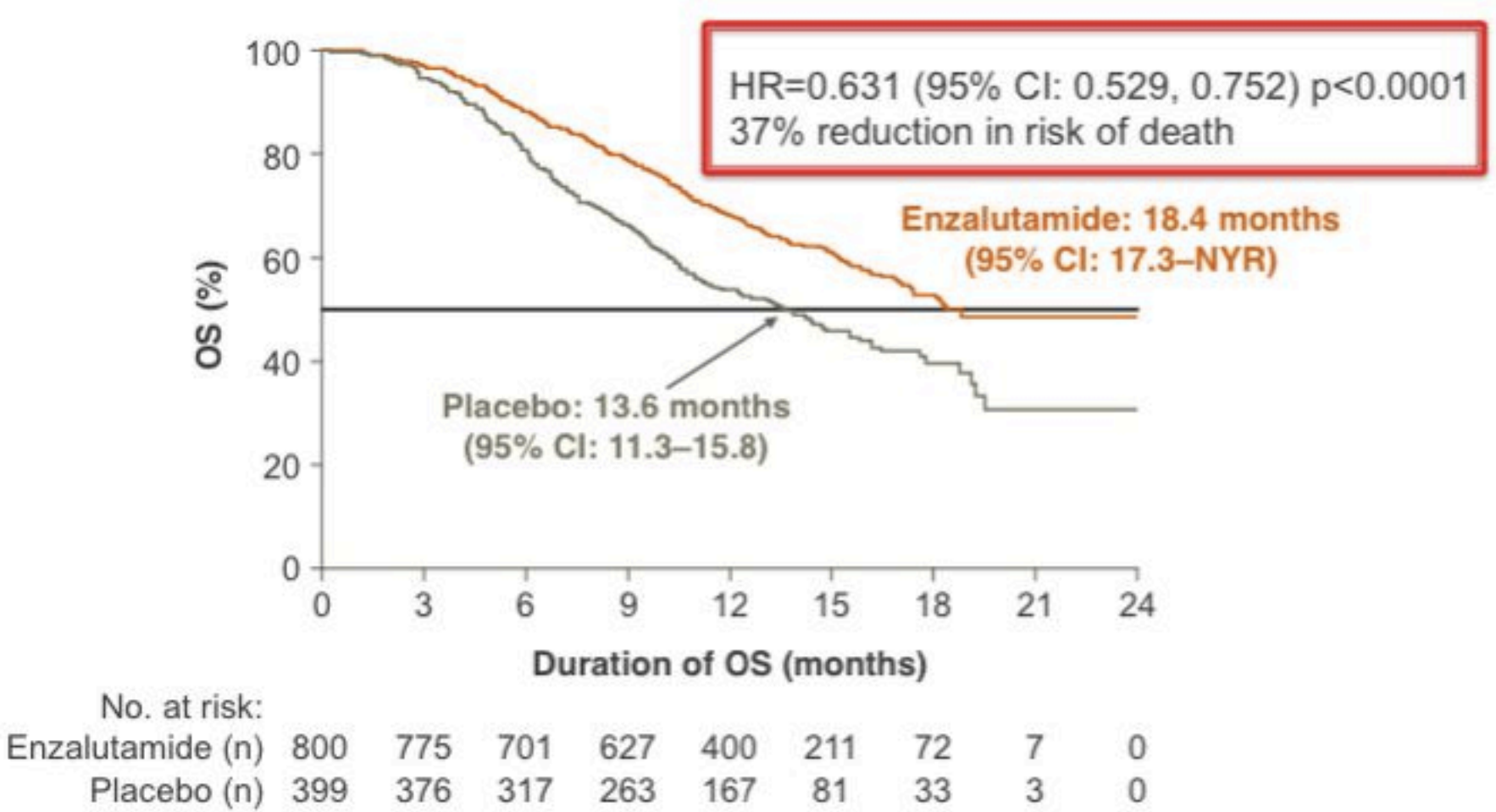
Scher HI et al., N Engl J Med 2012

COU-AA-301 Overall Survival
Median Benefit 4.6 Months



De Bono J et al., N Engl J Med 2011; 346(21):1995-200

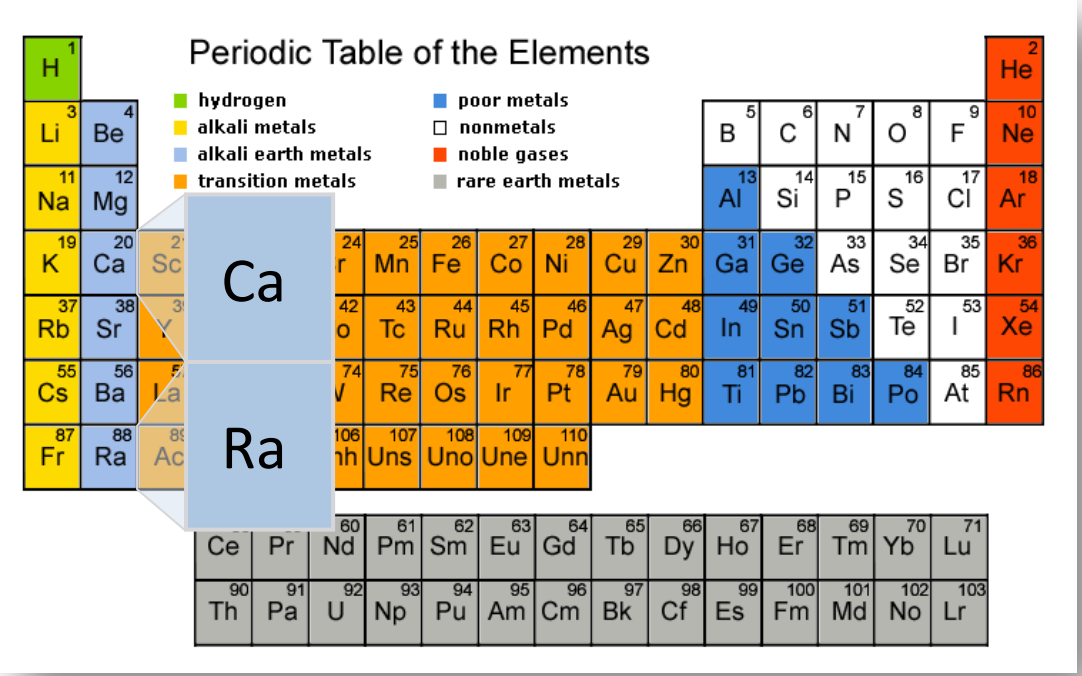
AFFIRM Overall Survival
Median Benefit 4.8 Months



Scher HI et al., N Engl J Med 2012; 367:1187-97

Radium-223 Targets Bone Metastases

- Radium-223 functions as a calcium mimic
- Targets sites of new bone growth within and around bone metastases
- Excreted by the small intestine

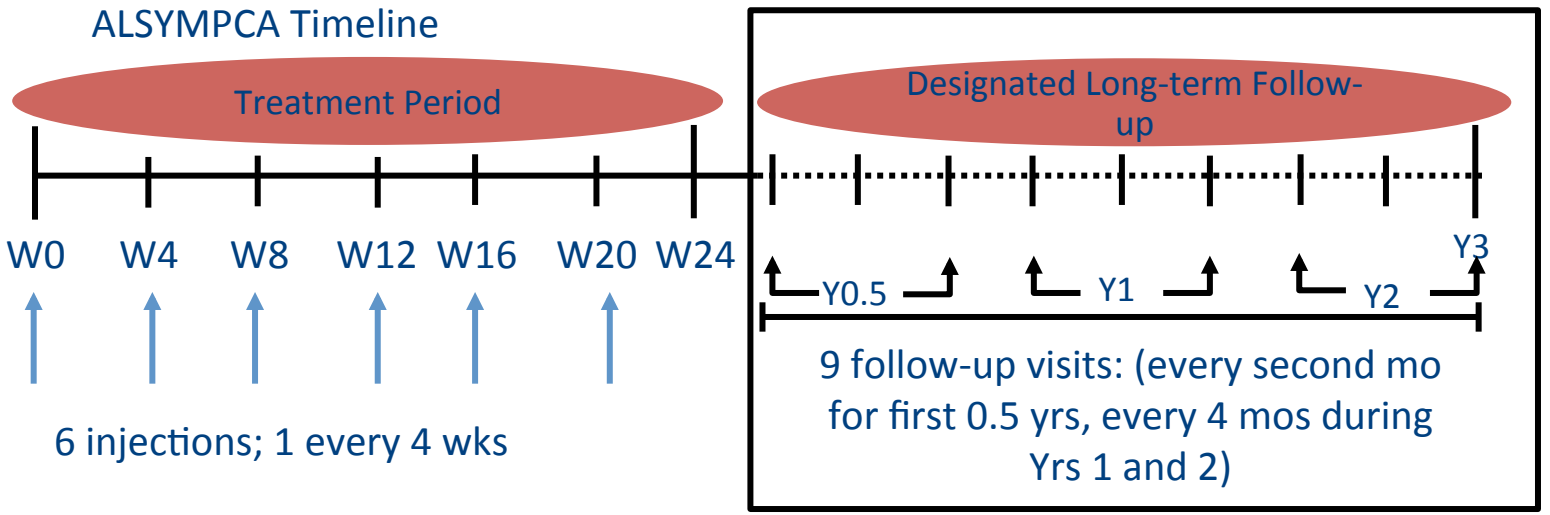


The 'ALSYMPCA' trial

Patients with:
- Confirmed symptomatic CRPC
- ≥ 2 bone metastases
- No known visceral metastases
- Post-docetaxel or unfit for docetaxel (N = 921)

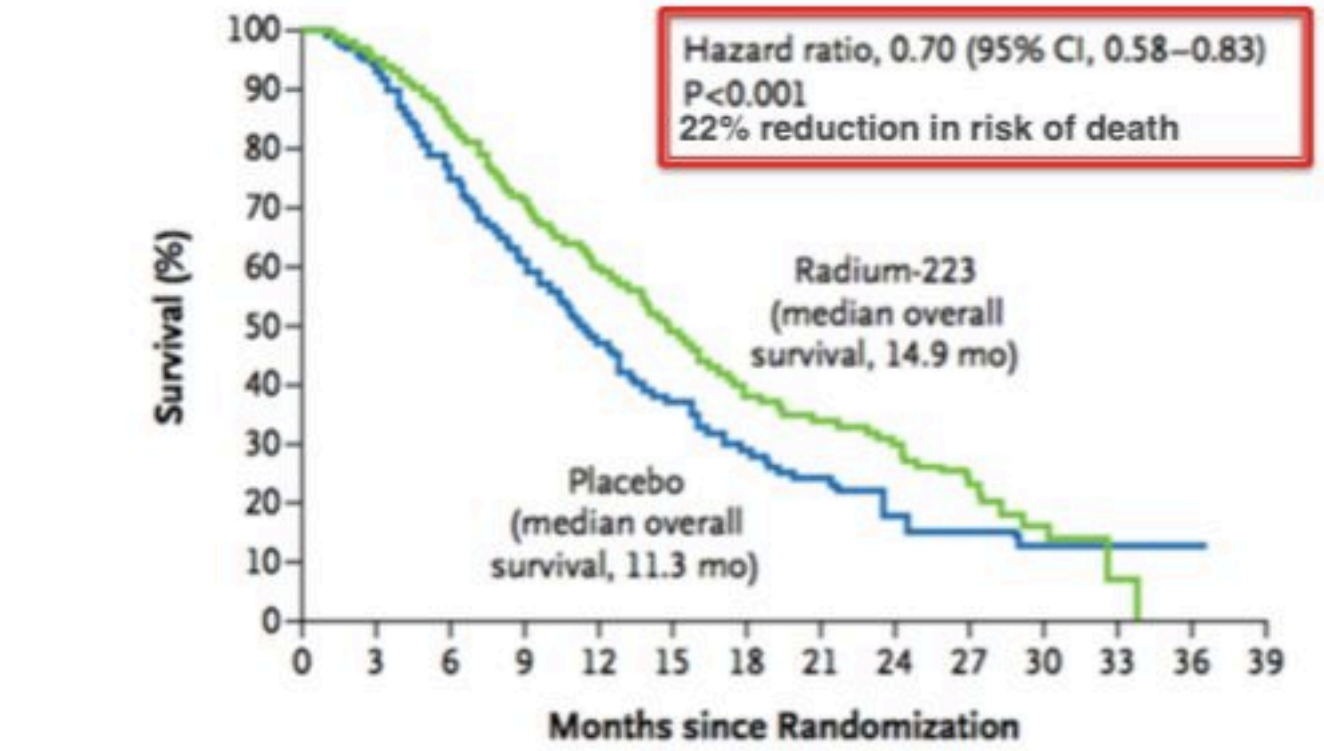
Radium-223 50 kBq/kg + Best Standard of Care

Placebo (saline) + Best Standard of Care



Parker et al., N Engl J Med 2013; 18;369(3):213-23

ALSYMPCA Overall Survival
3.6 months improvement vs placebo



No. at Risk														
Radium-223	614	578	504	369	274	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	103	67	39	24	14	7	4	2	1	0

Parker et al., N Engl J Med 2013; 18;369(3):213-23

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Radium-223 (N = 614)	Placebo (N = 307)
Age		
Median (range) — yr	71 (49–90)	71 (44–94)
>75 yr — no. (%)	171 (28)	90 (29)
White race — no. (%)†	575 (94)	290 (94)
Total alkaline phosphatase — no. (%)		
<220 U/liter	348 (57)	169 (55)
≥220 U/liter	266 (43)	138 (45)
Current use of bisphosphonates — no. (%)		
Yes	250 (41)	124 (40)
No	364 (59)	183 (60)
Any previous use of docetaxel — no. (%)		
Yes	352 (57)	174 (57)
No	262 (43)	133 (43)
ECOG performance-status score — no. (%)‡		
0	165 (27)	78 (25)
1	371 (60)	187 (61)
≥2	77 (13)	41 (13)
WHO ladder for cancer pain — no. (%)§		
1	257 (42)	137 (45)
2	151 (25)	78 (25)
3	194 (32)	90 (29)
Extent of disease — no. (%)		
<6 metastases	100 (16)	38 (12)
6–20 metastases	262 (43)	147 (48)
>20 metastases	195 (32)	91 (30)
Superscan¶	54 (9)	30 (10)

Parker et al., N Engl J Med 2013; 18;369(3):213-23

The 'ALSYMPCA' trial: Treatment-Related Hematologic Aes Long-term Follow-up

- All nonhematologic tx-related AEs < 1% in both groups
- Tx-related aplastic anemia in 1 radium-223 patient
- No reports of AML, MDS, or primary bone cancer
- Primary cancers in other organs: 2 in radium-223, 3 in placebo; non-tx related

Posttreatment AE, n (%)	Radium-223 (n = 404)			Placebo (n = 167)		
	All Grades	Grade 3/4	Grade 5	All Grades	Grade 3/4	Grade 5
Anemia	11 (3)	5 (1)	0	5 (3)	1 (1)	0
Aplastic anemia	1 (< 1)	1 (< 1)	0	0	0	0
Leukopenia	2 (< 1)	2 (< 1)	0	0	0	0
Neutropenia	2 (< 1)	2 (< 1)	0	0	0	0
Thrombocytopenia	4 (1)	0	0	0	0	0

Nilsson S, et al. ASCO GU 2014. Abstract 9

The 'ALSYMPCA' trial: Long-term Follow-up

- In 1.5-yr postinjection follow-up of patients (n = 404) with mCRPC treated with radium-223:
  - Myelosuppression remained low (≤ 3%)
  - No reports of AML, MDS, or primary bone cancer
  - No additional safety issues identified

Nilsson S, et al. ASCO GU 2014. Abstract 9

Randomized Phase IIa: Study of Radium-223 With Docetaxel vs Docetaxel

- **Patients with:**
- Confirmed symptomatic CRPC
- ≥ 2 bone metastases
- Eligible for docetaxel
- Excluded for > 2 lung/liver metastases (≥ 2 cm)

- (N = 60)

Randomized 2:1

Radium-223 50 kBq/kg q6w + Docetaxel 60 mg/m^2 q3w

Docetaxel 75 mg/m^2 q3w

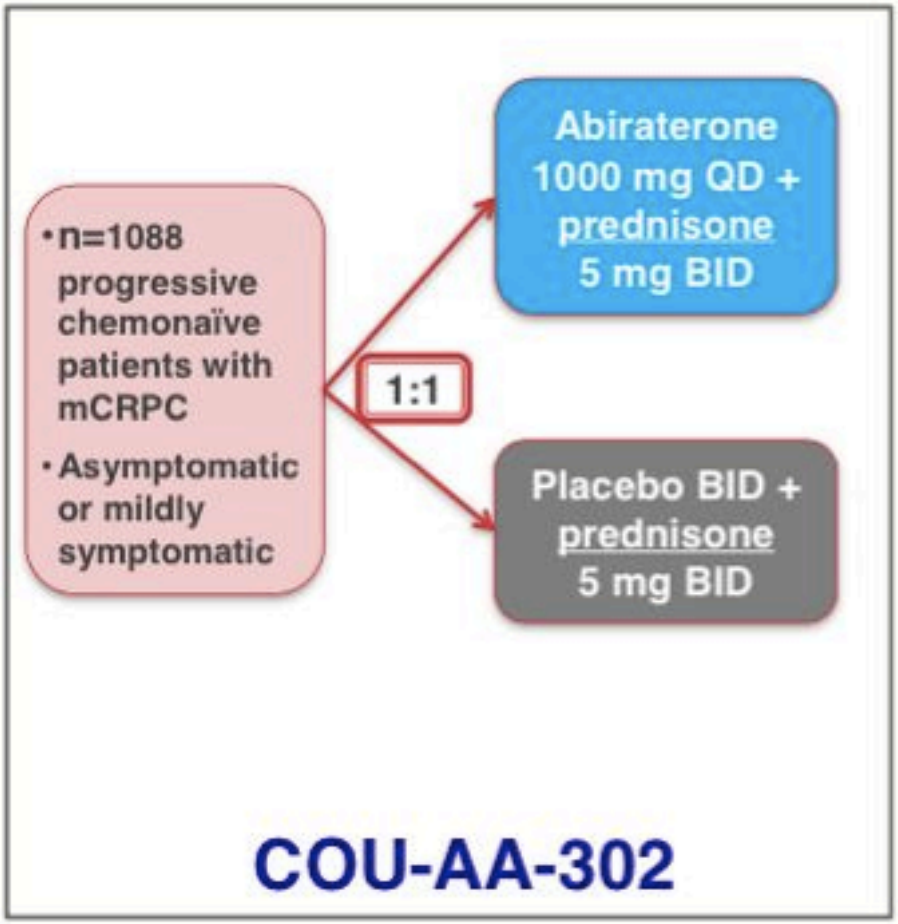
Morris MJ, et al. ASCO 2013. Abstract 5021. ClinicalTrials.gov. NCT01106352.

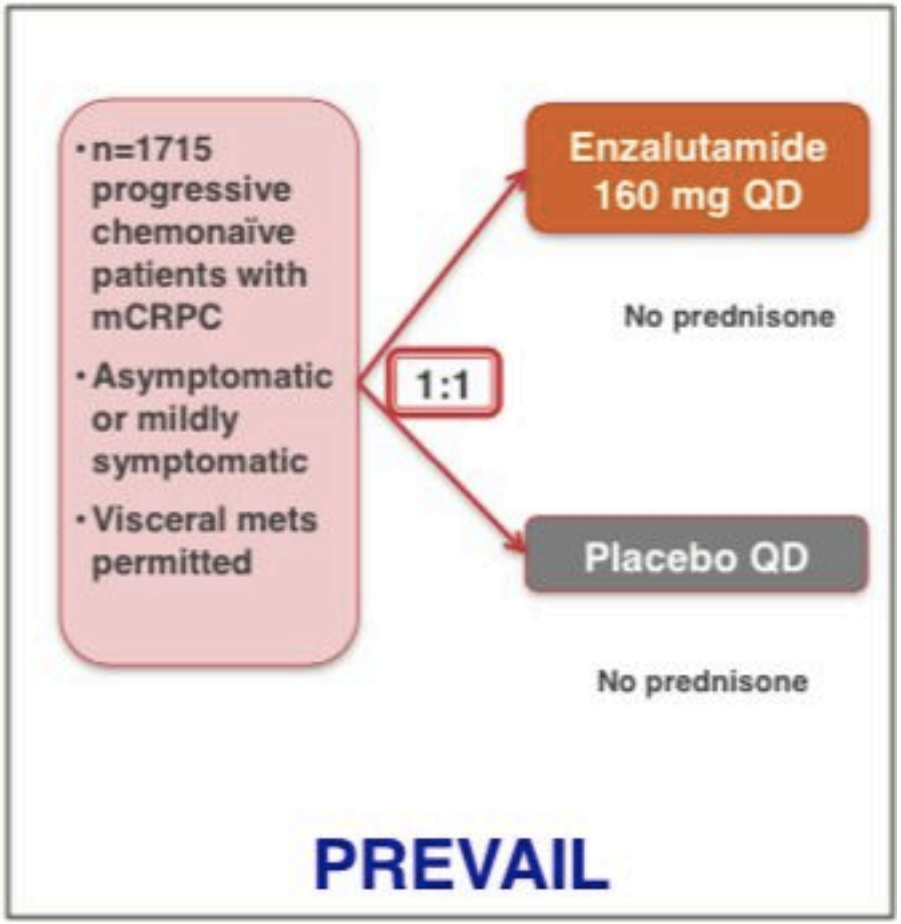
Post-Doc options that improve survival

Trial	Disease State	Trial Design	HR for OS	Survival (months)
TROPIC[1] N=755	Post docetaxel	Cabazitaxel/prednisone vs. mitoxantrone/prednisone	0.70	15.1 vs. 12.7
COU-AA-301[2] N=1195	Post docetaxel	Abiraterone/prednisone vs. placebo/prednisone	0.74	15.8 vs. 11.2
AFFIRM[3] N=1199	Post docetaxel	MDV3100 vs. placebo	0.63	18.4 vs. 13.6
ALSYMPCA[4] N=921	Post docetaxel (or unsuitable)	Ra223/BSC vs. placebo/BSC	0.70	14.9 vs. 11.3

[1]De Bono et al. *Lancet*, 2010, 376:1147-54
[2]De Bono J et al., N Engl J Med 2011; 346(21):1995-200
[3]Scher HI et al., N Engl J Med 2012; 367:1187-97
[4]Parker et al., N Engl J Med 2013; 18;369(3):213-23

Abiraterone and Enzalutamide in mCRPC
Phase III Study Pre-Docetaxel
Primary end point: OS

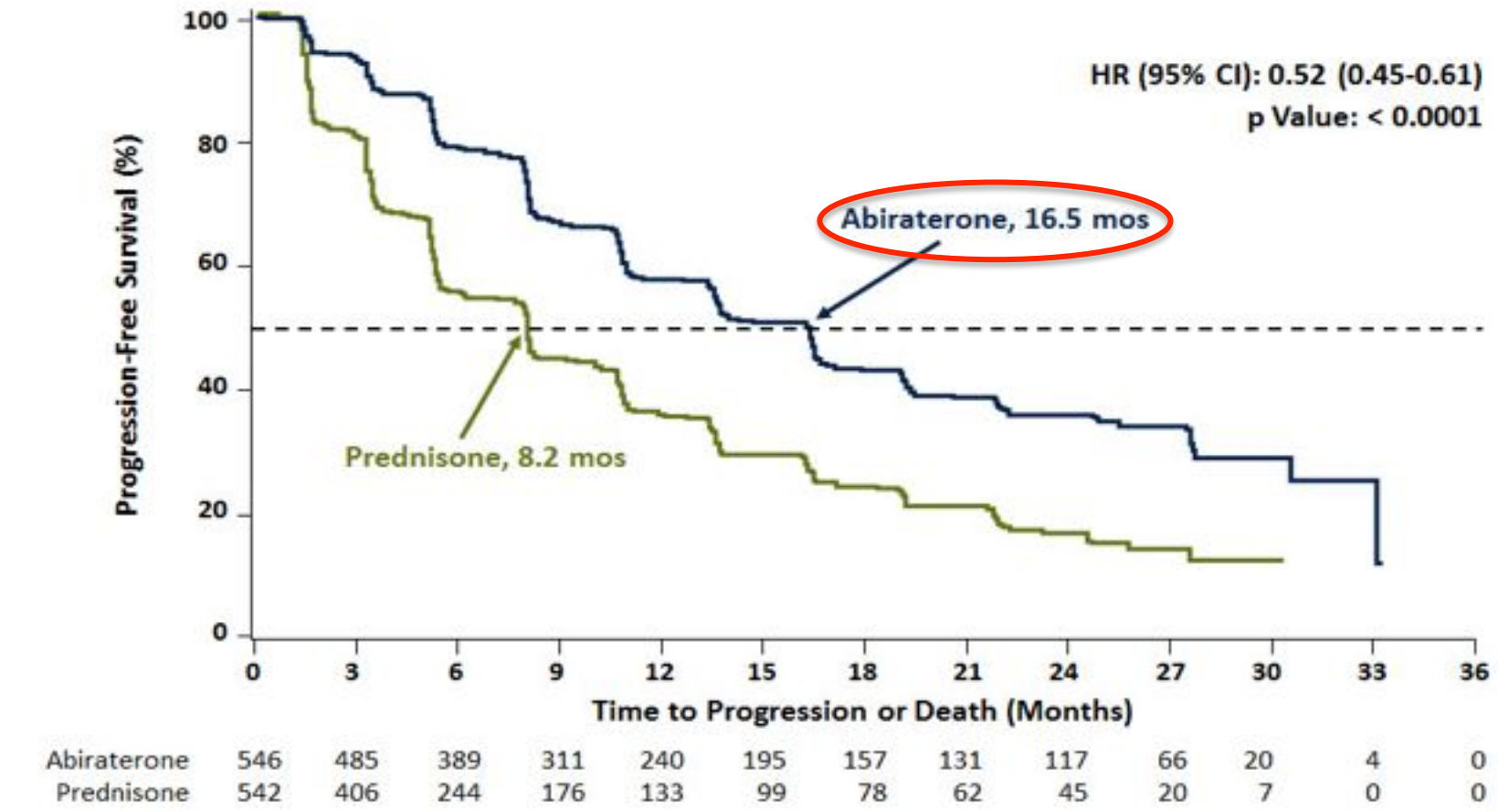




Ryan C, et al. NEJM 2013

Beer TM et al., N Engl J Med 2014

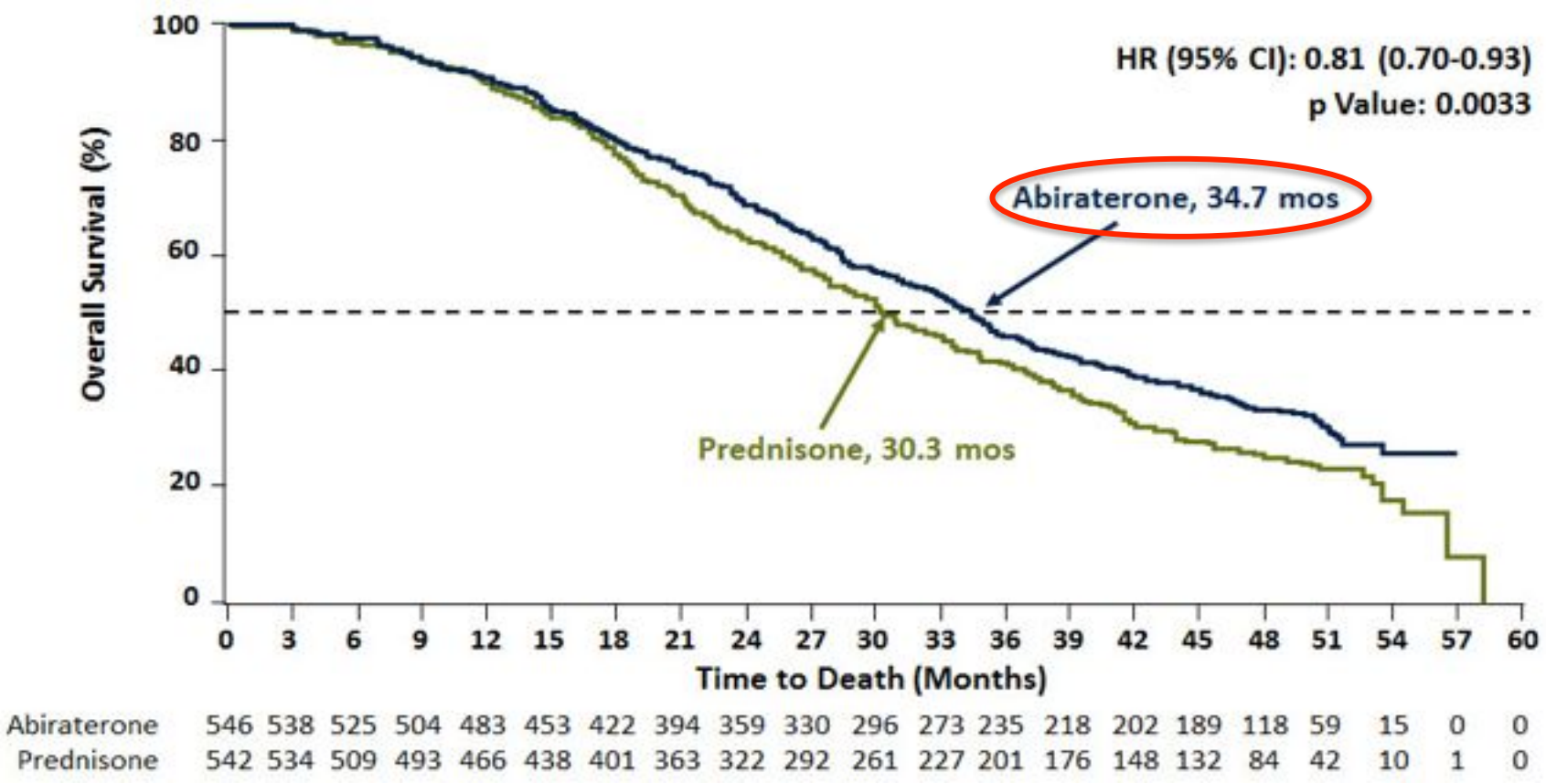
Abiraterone Doubled Time to rPFS1



Third interim analysis data. rPFS assessed by investigator review at prespecified IA.

Rathkopf DE et al. Eur Urol 2014; [Epub]

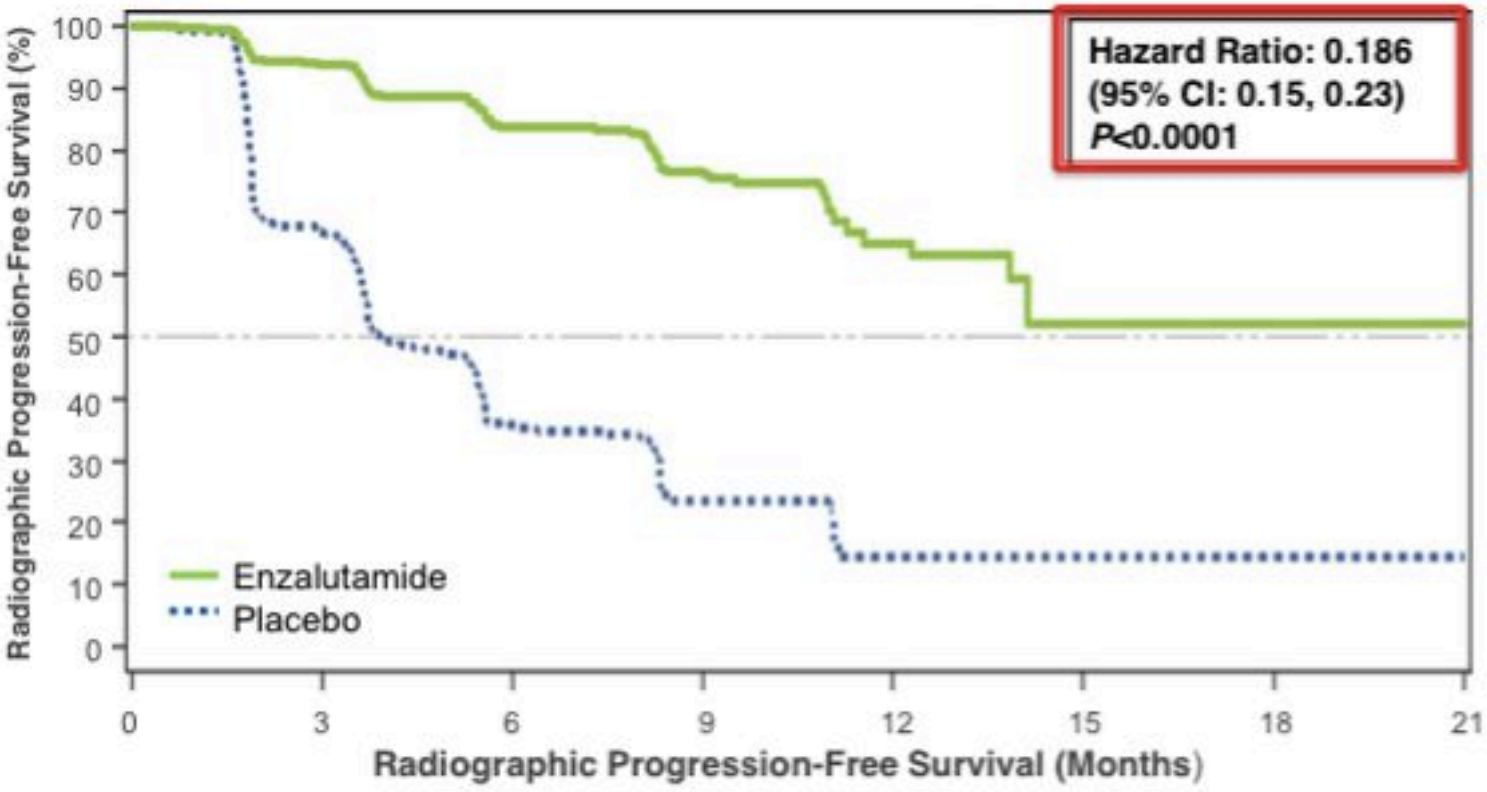
COU-AA-302: Final OS Analysis



- Median follow-up of 49.2 months
- Abiraterone treatment effect more pronounced when adjusting for 44% of prednisone patients who received subsequent abiraterone (HR = 0.74)

Ryan C et al. ESMO 2014; Abstract 7530 (oral presentation)

PREVAIL: Enzalutamide 81% Decrease in Risk of Progression



Patients at Risk

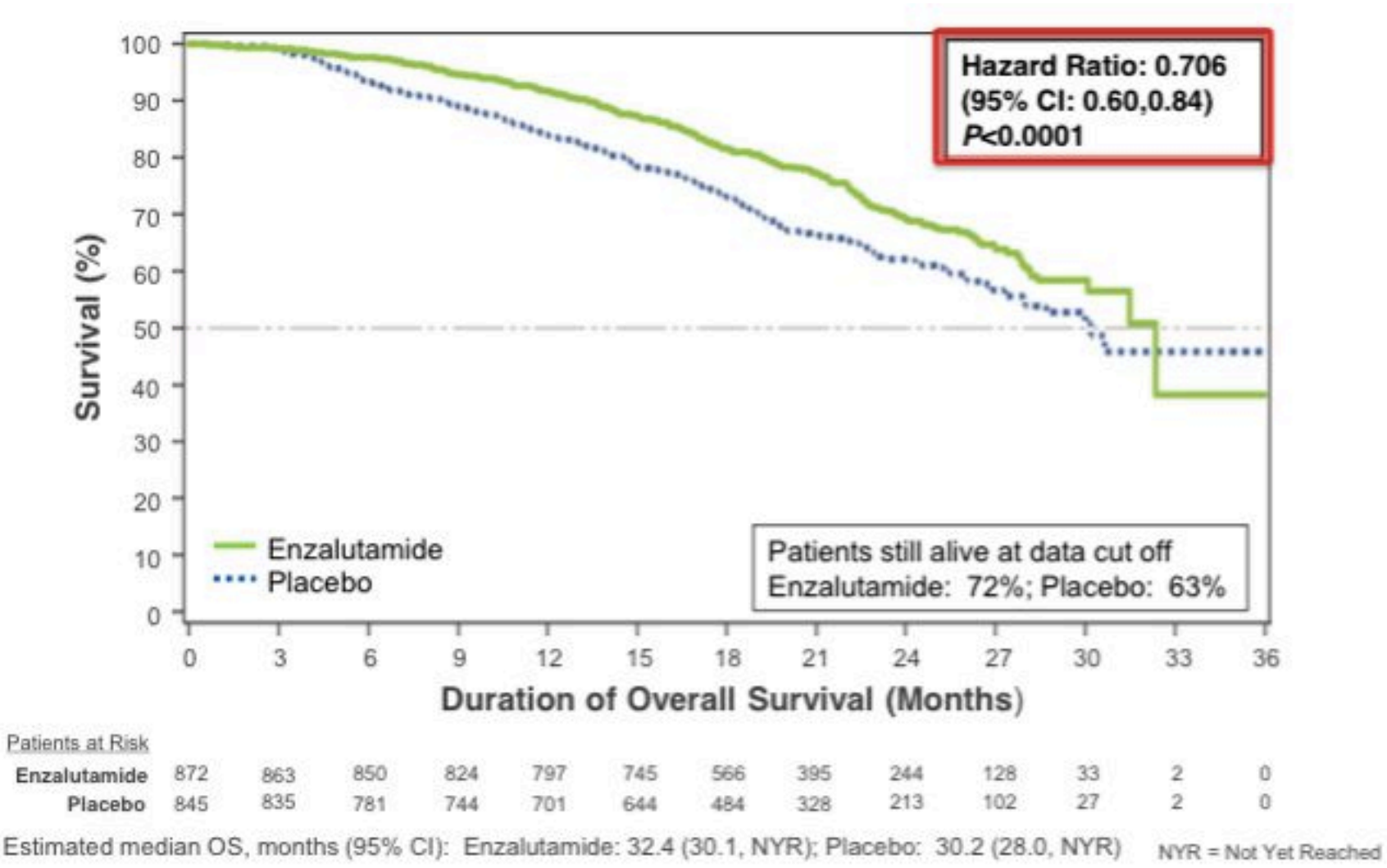
Enzalutamide	832	514	256	128	34	5	1	0
Placebo	801	305	79	20	5	0	0	0

Estimated median rPFS, months (95% CI): Enzalutamide: NYR (13.8, NYR); Placebo: 3.9 (3.7, 5.4)

NYR = Not Yet Reached

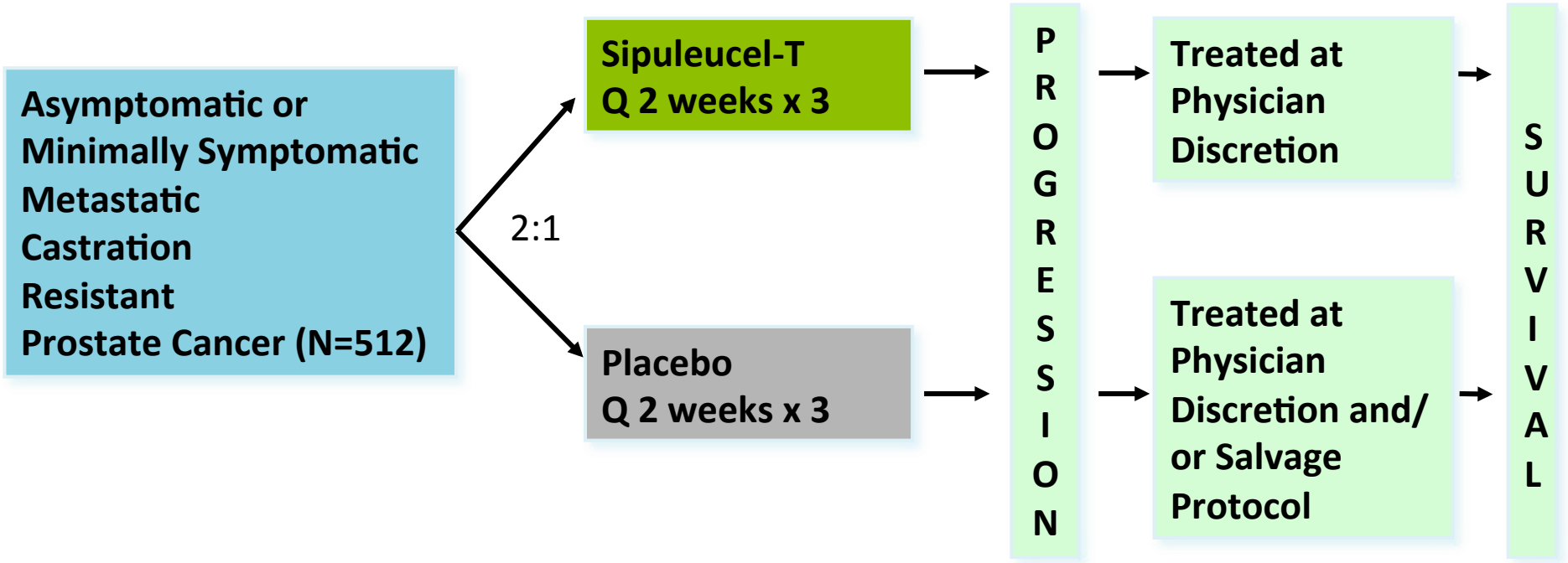
Beer TM et al., N Engl J Med 2014 Jul 31; 371(5):424-33

PREVAIL: Enzalutamide Reduced Risk of Death by 29%



Beer TM et al., N Engl J Med 2014 Jul 31; 371(5):424-33

Randomized Phase 3 IMPACT Trial (IMmunotherapy Prostate AdenoCarcinoma Treatment)

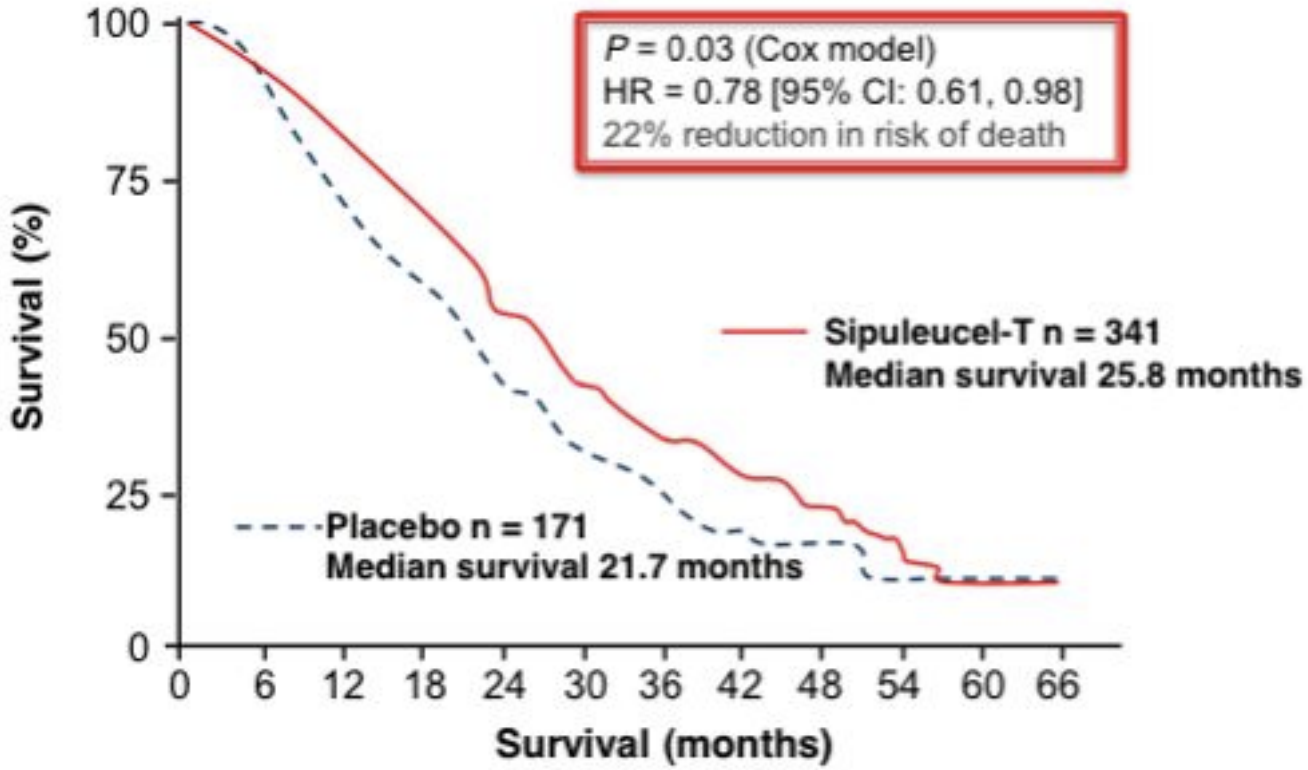


Primary Endpoint: Overall Survival

Secondary Endpoint: Objective Disease Progression

Kantoff et al., N Engl J Med 2010; 363(5):411-22

IMPACT Overall Survival
4.1 months improvement vs placebo



Kantoff et al., N Engl J Med 2010; 363(5):411-22

Pre-Doc options that improve survival

Trial	Visceral Disease Allowed	Trial Design	HR for OS	Survival (months)
TAX327[1]	YES	Docetaxel/prednisone vs. mitoxantrone/prednisone	0.79	18.9 vs. 16.5
COU-AA-302[2]	NO	Abiraterone/prednisone vs. placebo/prednisone	0.81	34.7 vs. 30.3
PREVAIL[3]	NO	Enzalutamide vs. placebo	0.70	32.4 vs. 30.4
ALSYMPCA[4]	NO	Ra223/BSC vs. placebo/BSC	0.70	16.1 vs. 11.5
IMPACT[5]	NO	Sipuleucel-T vs placebo	0.78	25.8 vs. 21.7

[1]Tannock IF, NEJM 2004; 351(15):1502-12
[2]Ryan C et al. ESMO 2014; Abstract 7530 (oral presentation)
[3]Beer TM et al., N Engl J Med 2014 Jul 31; 371(5):424-33
[4]Parker et al., N Engl J Med 2013; 18;369(3):213-23
[5]Kantoff et al., N Engl J Med 2010; 363(5):411-22

Drug Resistance

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

AR-V7 and Resistance to Enzalutamide and Abiraterone in Prostate Cancer

Emmanuel S. Antonarakis, M.D., Changxue Lu, Ph.D., Hao Wang, Ph.D., Brandon Luber, Sc.M., Mary Nakazawa, M.H.S., Jeffrey C. Roeser, B.S., Yan Chen, Ph.D., Tabrez A. Mohammad, Ph.D., Yidong Chen, Ph.D., Helen L. Fedor, B.S., Tamara L. Lotan, M.D., Qizhi Zheng, M.D., Angelo M. De Marzo, M.D., Ph.D., John T. Isaacs, Ph.D., William B. Isaacs, Ph.D., Rosa Nadal, M.D., Channing J. Paller, M.D., Samuel R. Denmeade, M.D., Michael A. Carducci, M.D., Mario A. Eisenberger, M.D., and Jun Luo, Ph.D.

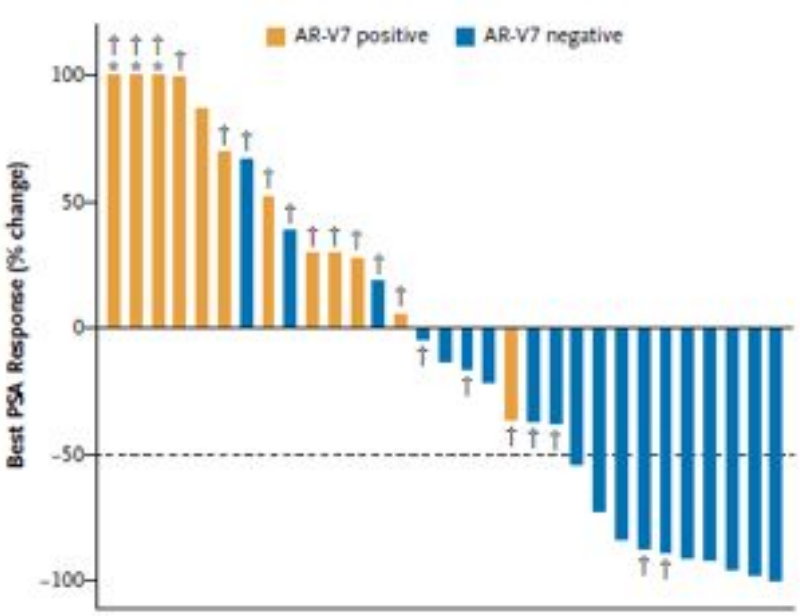
AR-V7 as a predictor of treatment outcome to enzalutamide and abiraterone in mCRPC

AR-V7 characteristics:

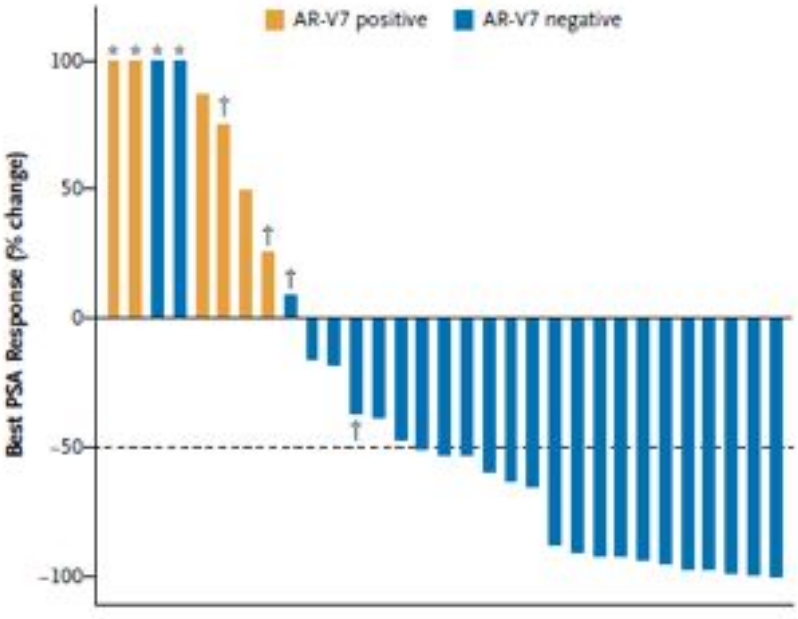
- Most abundant splice variant
- Costitutively active
- 20-fold increased expression in mCRPC
- Produces functional protein product unaffected by nonsense-mediated mRNA decay

Pelekanou V et al., Hormones 2013; 12:224- 35

RESULTS: PSA RESPONSE RATE



Enzalutamide-treated patients

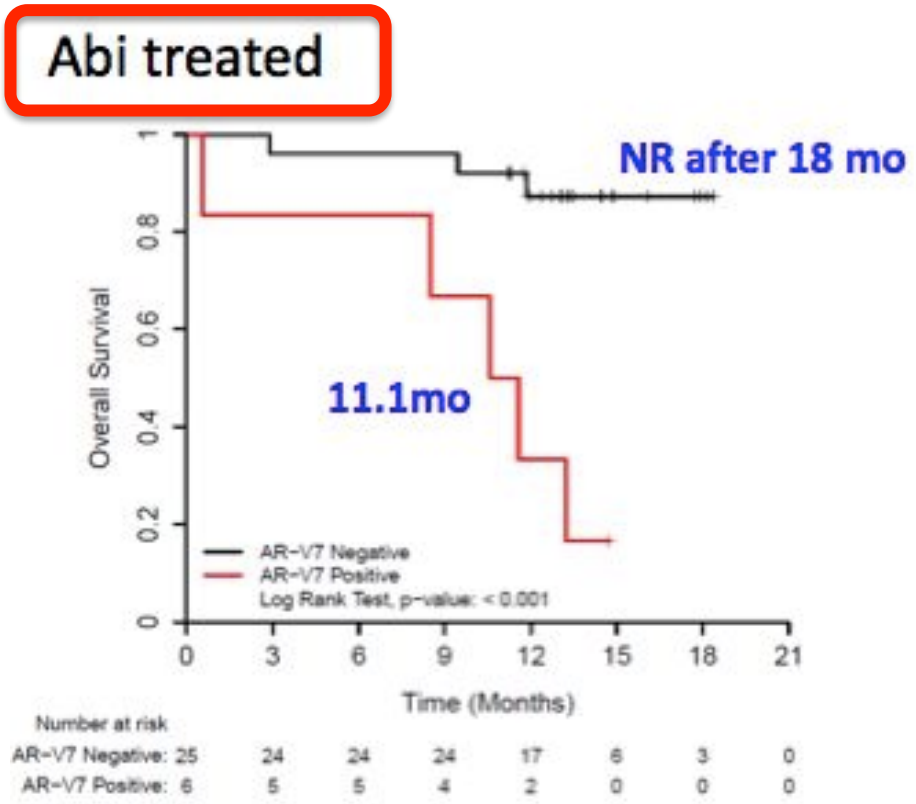


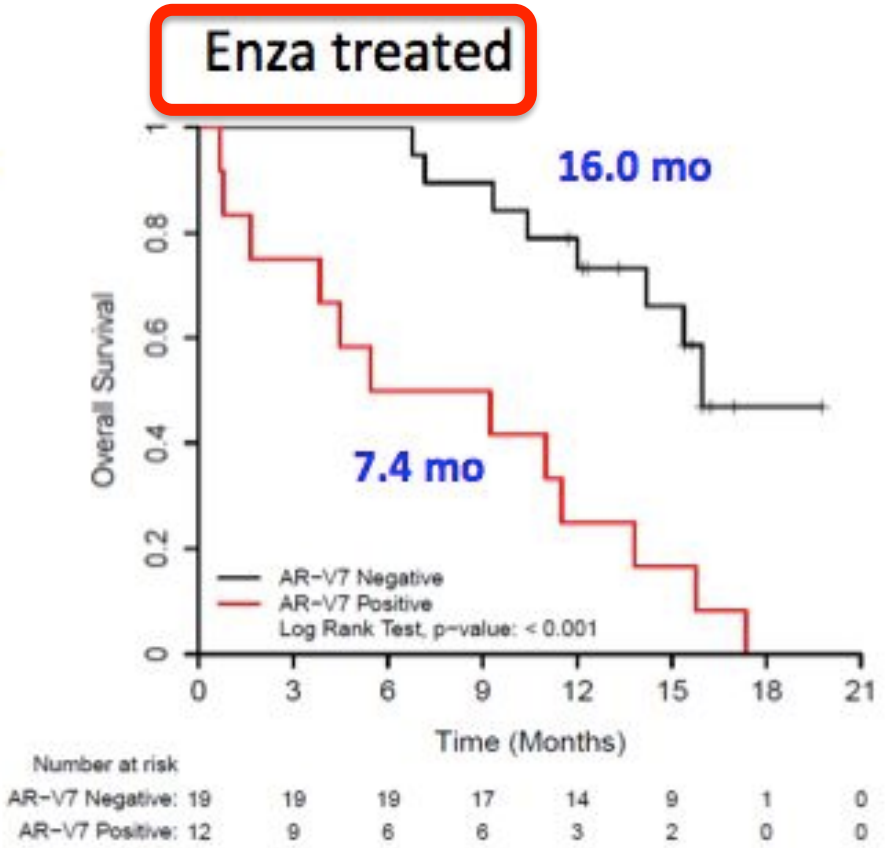
Abiraterone-treated patients

Among men receiving enzalutamide or abiraterone, AR-V7-positive patients had **lower PSA response rates** than AR-V7-negative patients (0% vs 53%, p=0.004 and 0% vs 68%, p=0.004, respectively).

Antonarakis et al., NEJM 2014.

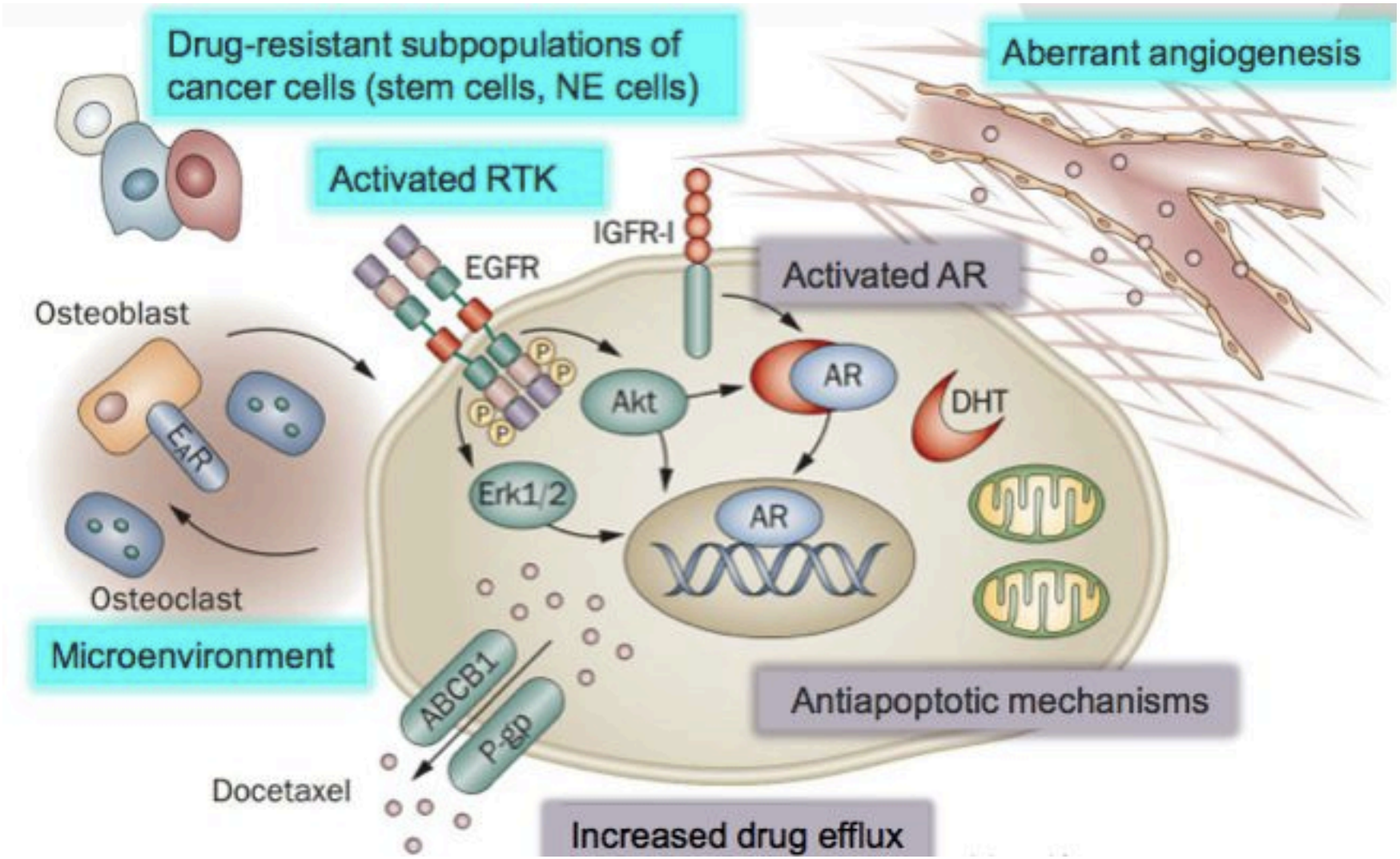
OS Results per ARV7 status





Antonarakis et al. ESMO 2014; Abstract 7980 (oral presentation)

Mechanisms of Resistance to Docetaxel in Metastatic Prostate Cancer



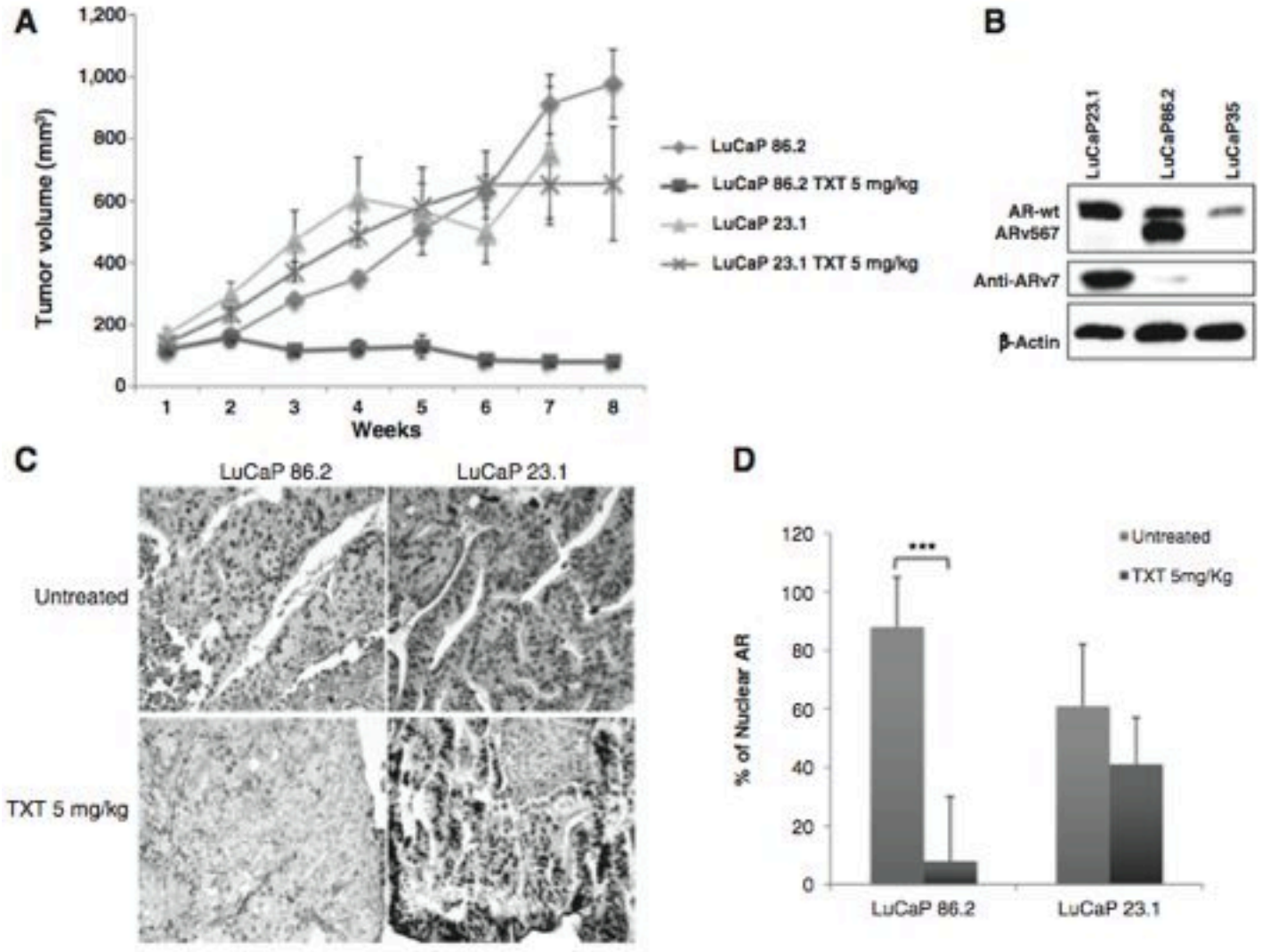
Adapted from Seruga et al, Nat. Rev. Clin. Oncol. 2011

What are the predictive biomarkers for Docetaxel response in mCRPC?

- **MDR1/ABCB1 ?** Drug-Efflux pump
- **β3-tubulin**
- **PTEN**
- **Recent potential candidates**
  - Notch signaling pathway

No predictive biomarker validated on human tumors

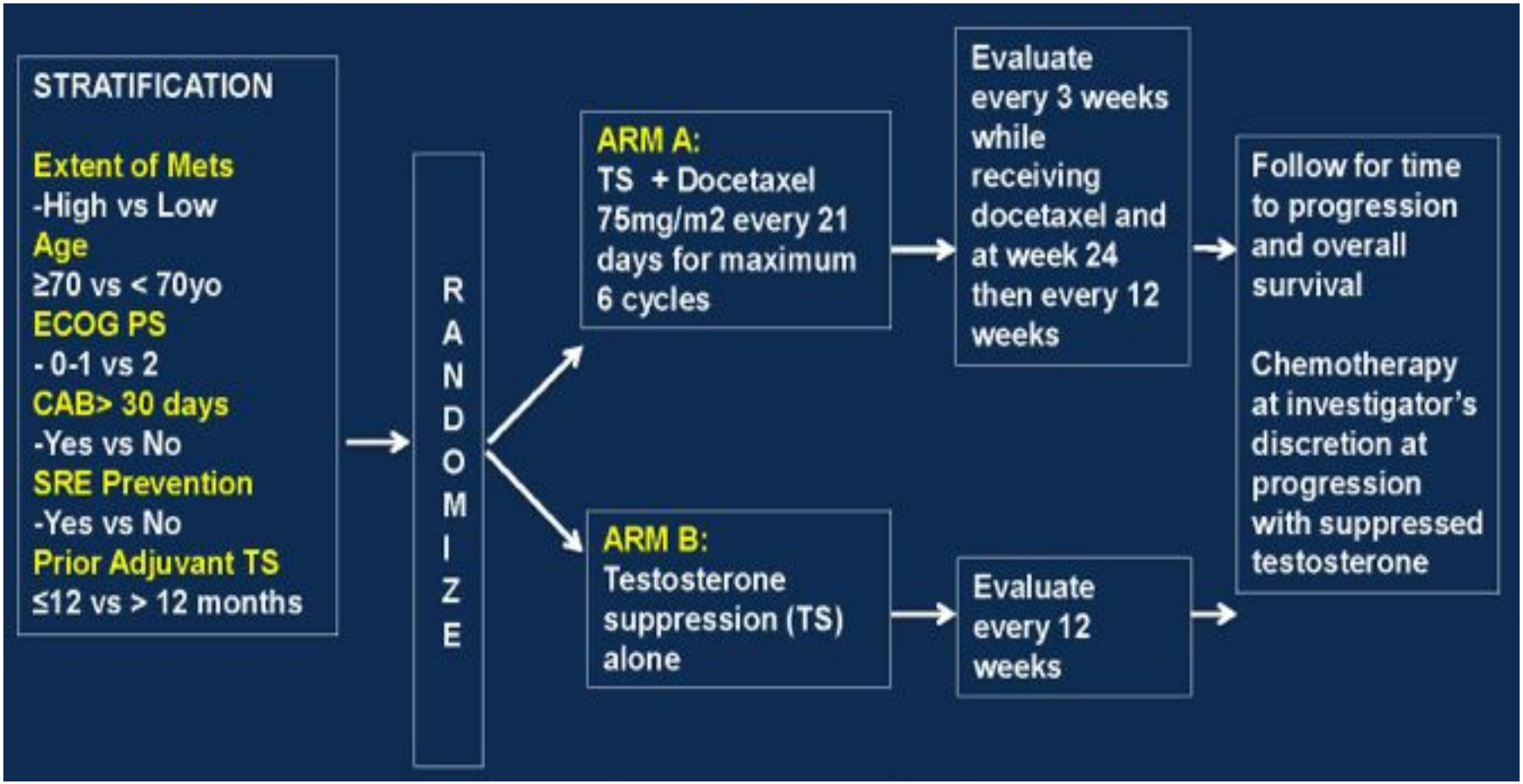
Androgen Receptor Splice Variants Determine Taxane Sensitivity in Prostate Cancer



Thadani-Mulero, Cancer Res 2014;74:2270-2282

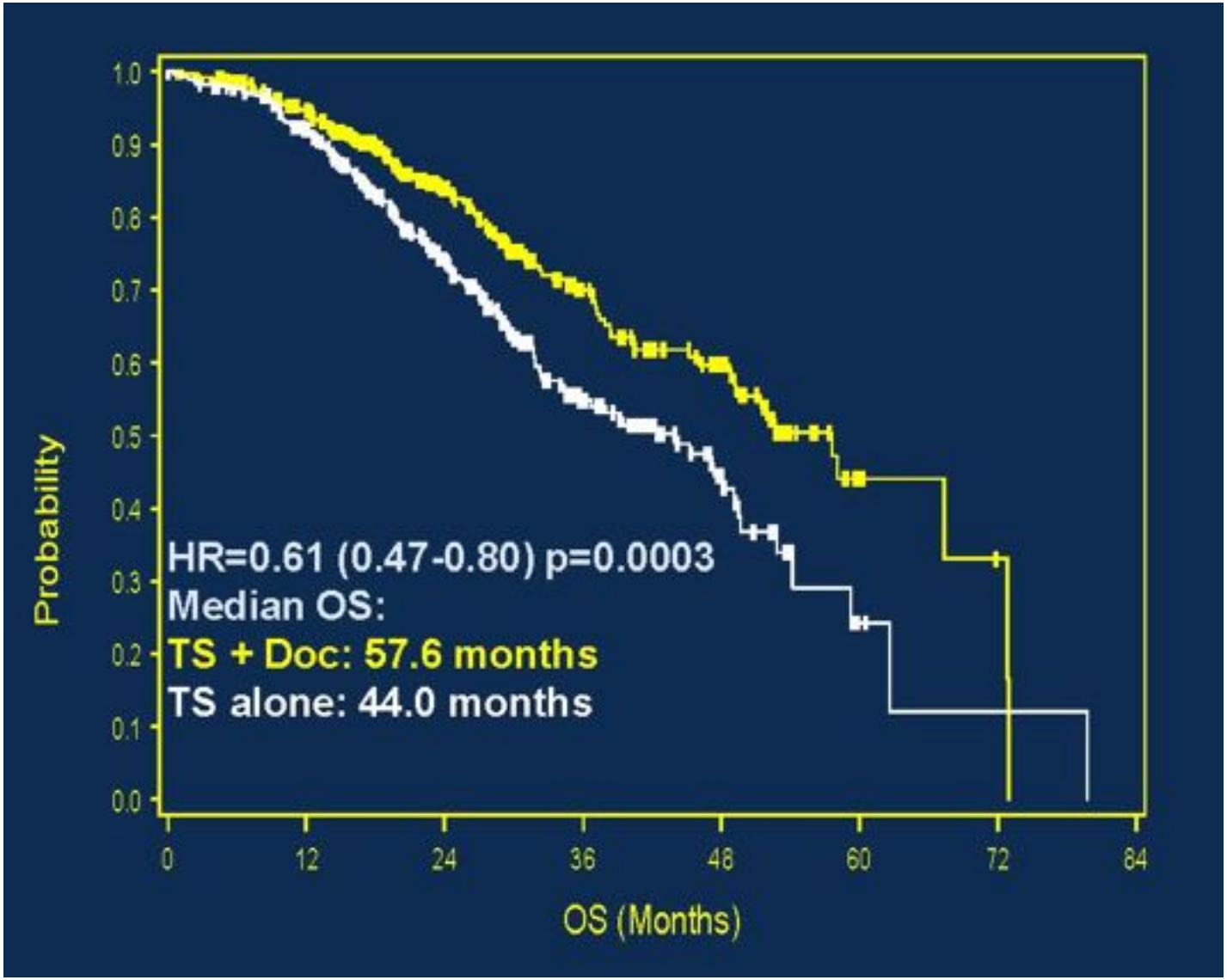
C. Sweeney Abs #LBA2 Plenary session June 1, 2014

E3805 – CHAARTED: Study Design



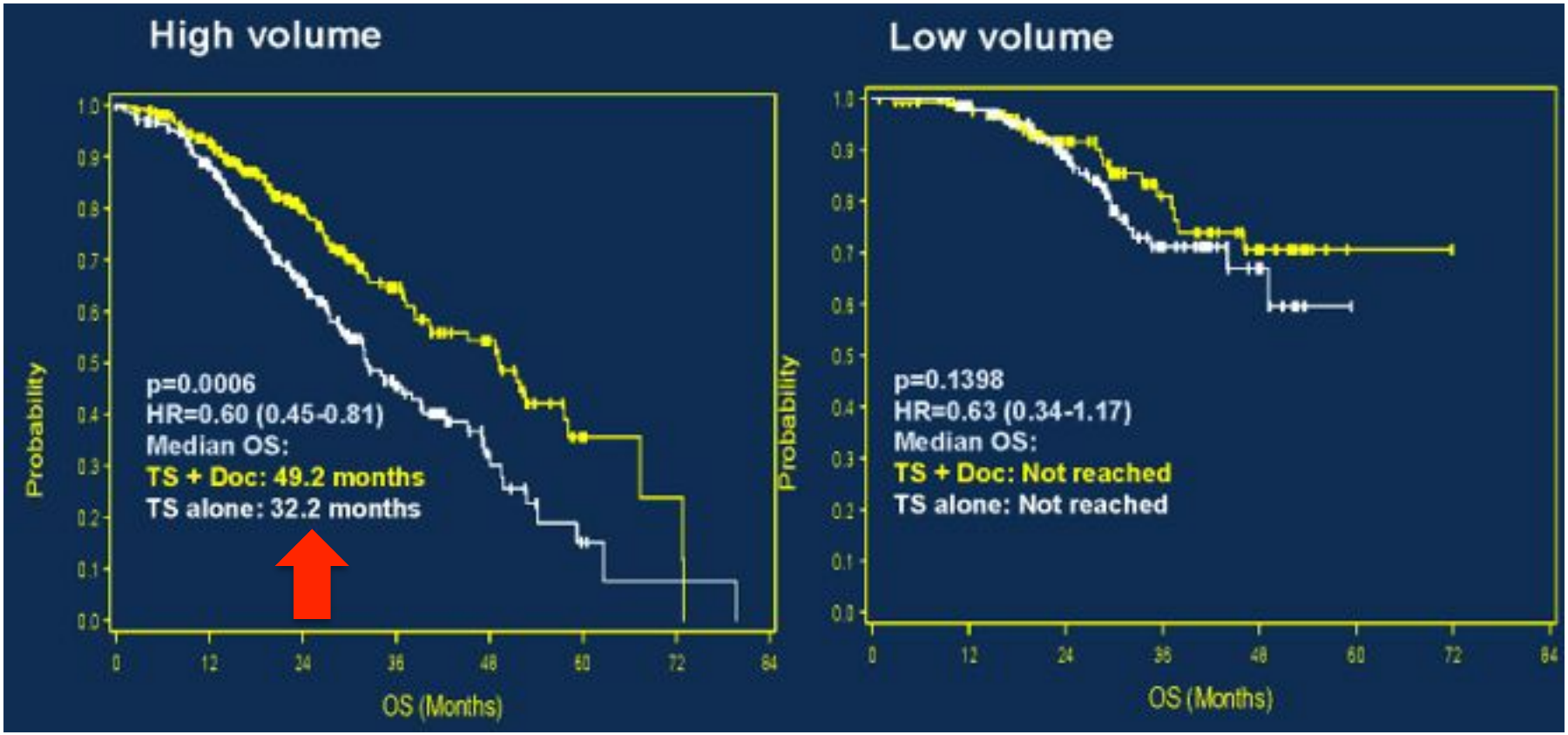
C. Sweeney Abs #LBA2 Plenary session June 1, 2014

E3805 – CHAARTED: Overall Survival



C. Sweeney Abs #LBA2 Plenary session June 1, 2014

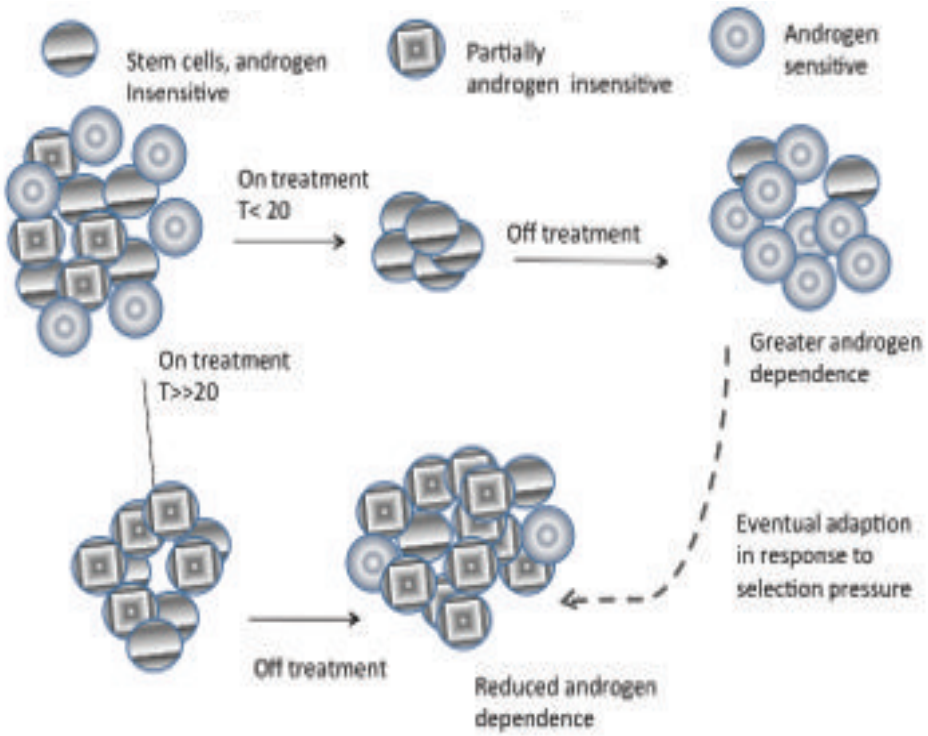
OS by extent of metastatic disease at start of ADT



In patients with high volume metastatic disease, testosterone suppression plus early docetaxel improves median overall survival by 17 months ***(32,2 vs 49,2)***

C. Sweeney Abs #LBA2 Plenary session June 1, 2014

Chemotherapy in hormone-sensitive PC: Rationale



L. Klotz, Curr Oncol, Vol. 19, pp. S13-21

- Pros
  - Attack de novo testosterone indipendent clones early – allow ADT to keep PrCa in remission longer
  - Some Patients at the time of progression are too frail for chemo
- Contras
  - ADT will take cells out of cycle and be less responsive to cytotoxics
  - Some Patients respond for a long time and never need chemotherapy

Modified by C. Sweeney Abs #LBA2 Plenary session June 1, 2014

Selection criteria?

Breast cancer (adj setting)

- ER/PGR pos *vs* neg
- Clinical/biological criteria (St.Gallen guidelines)
  - Ki67
  - HER2 status
  - ER status
  - PGR status

  - Luminal A – B
  - HER2 overexpression
  - Basal-like

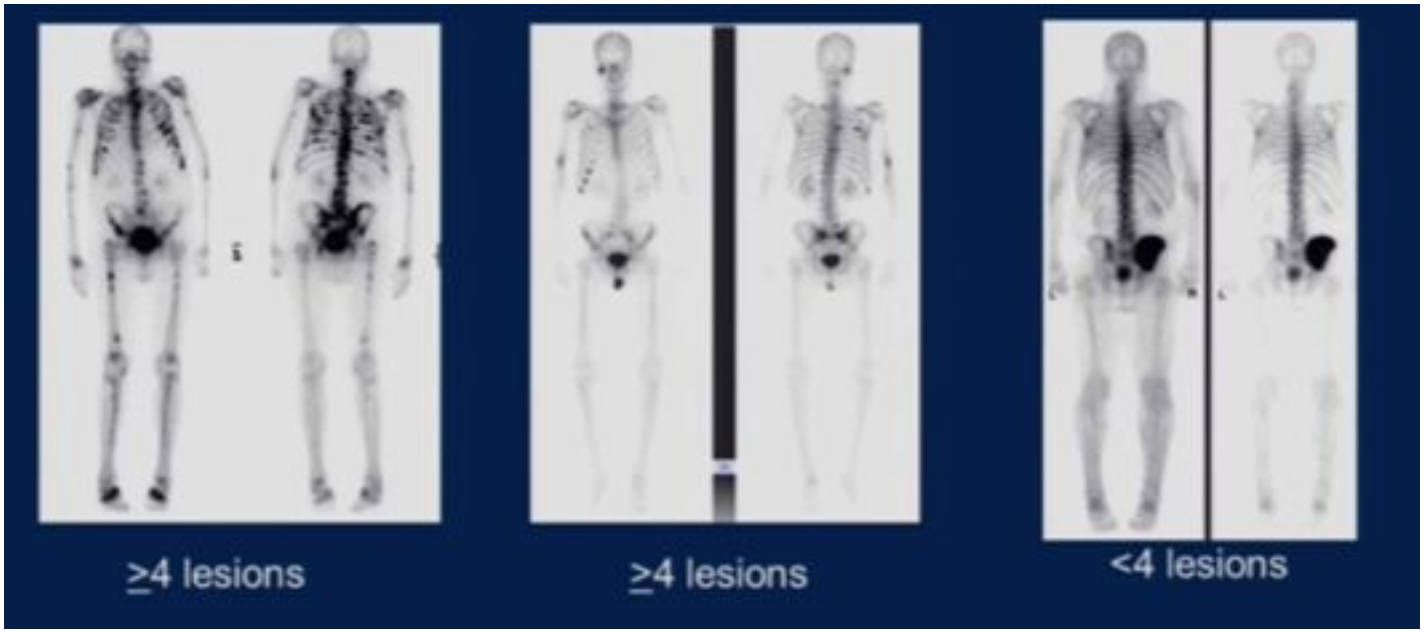
Prostate cancer

- DRE
- GS
- PSA

Courtesy of O. Caffo

CHAARTED definition of the risk

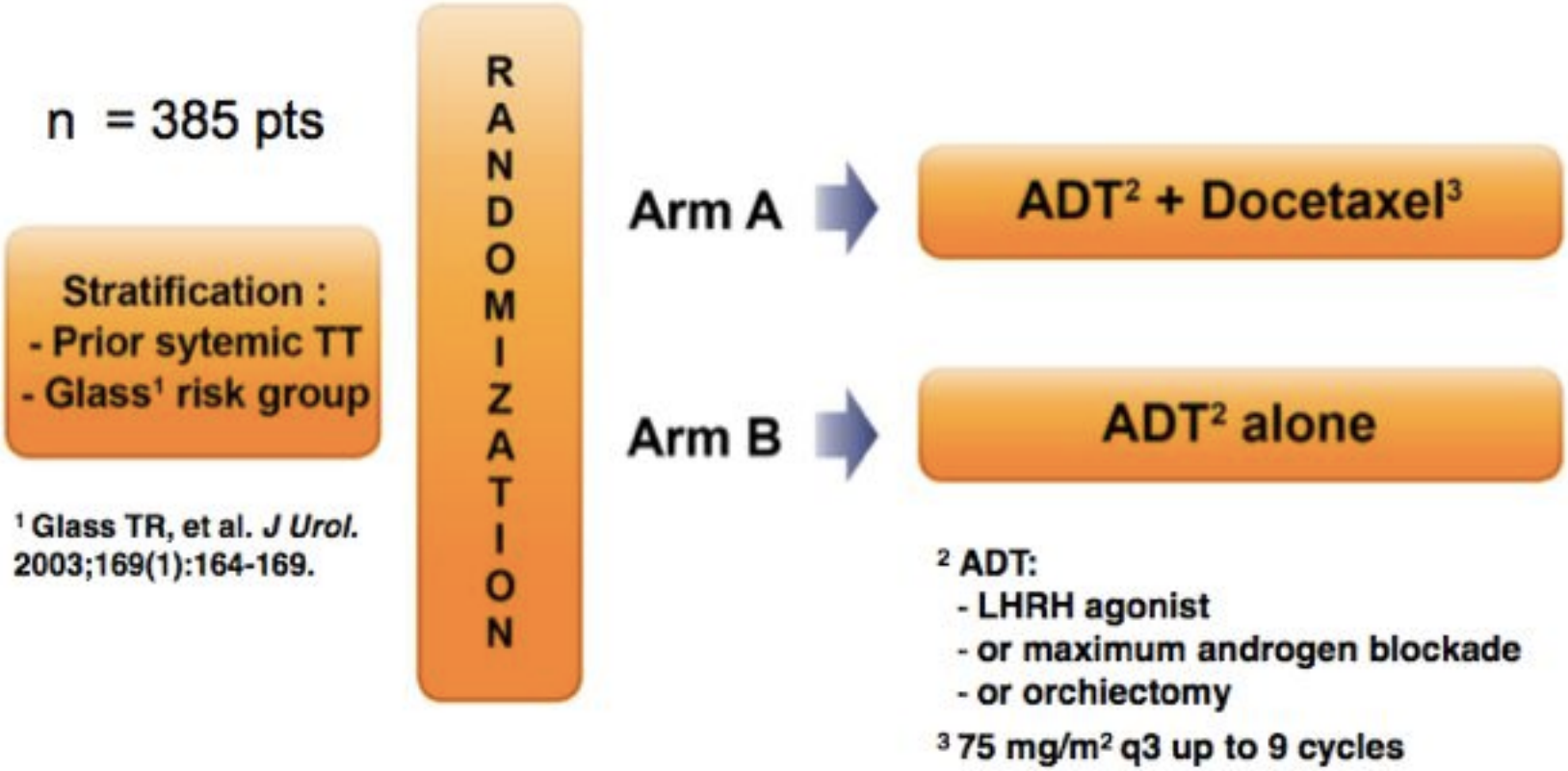
- High volume
  - Visceral mets and/or
  - ≥ 4 bone mets (at last 1 beyond pelvis and vertebral column)



Morris MJ Discussant Plenary session June 1, 2014

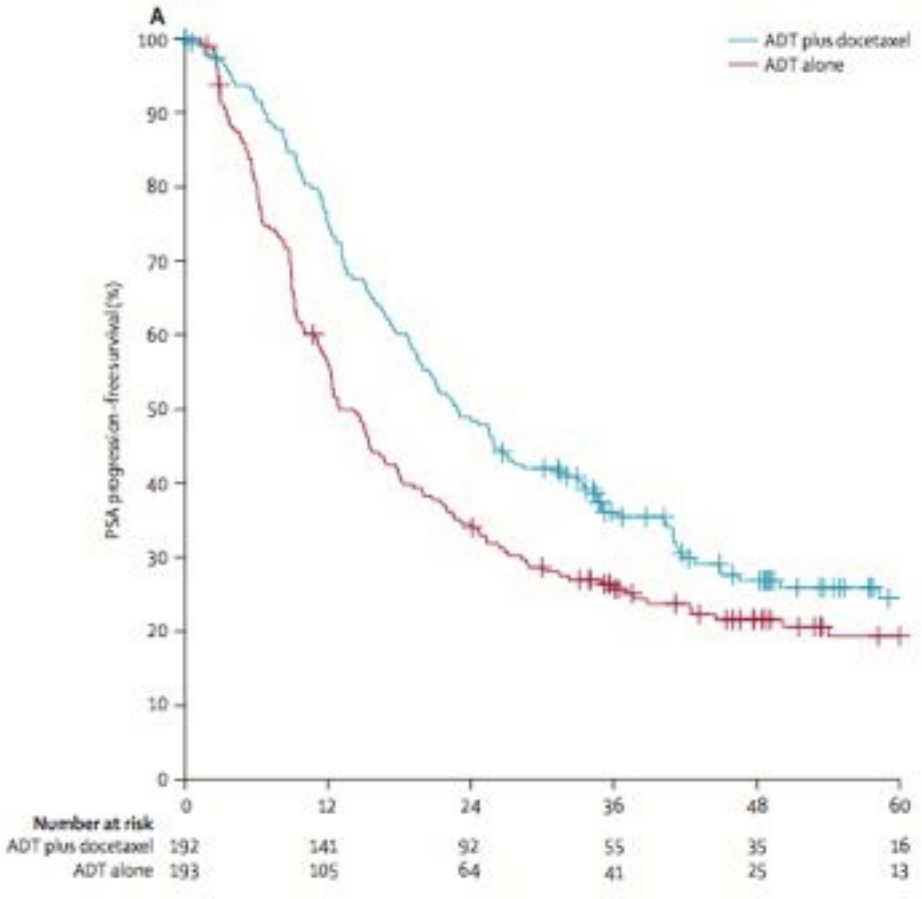
Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial

Gwenaelle Gravis, Karim Fizazi, Florence Joly, Stéphane Oudard, Franck Priou, Benjamin Esterni, Igor Latorzeff, Remy Delva, Ivan Krakowski, Brigitte Laguerre, Fréderic Rolland, Christine Théodore, Gael Deplanque, Jean Marc Ferrero, Damien Pouessel, Loïc Mourey, Philippe Beuzeboc, Sylvie Zanetta, Muriel Habibian, Jean François Berdah, Jerome Dauba, Marjorie Baciuchka, Christian Platini, Claude Linassier, Jean Luc Labourey, Jean Pascal Machiels, Claude El Kouri, Alain Ravaud, Etienne Suc, Jean Christophe Eymard, Ali Hasbini, Guilhem Bousquet, Michel Soulie

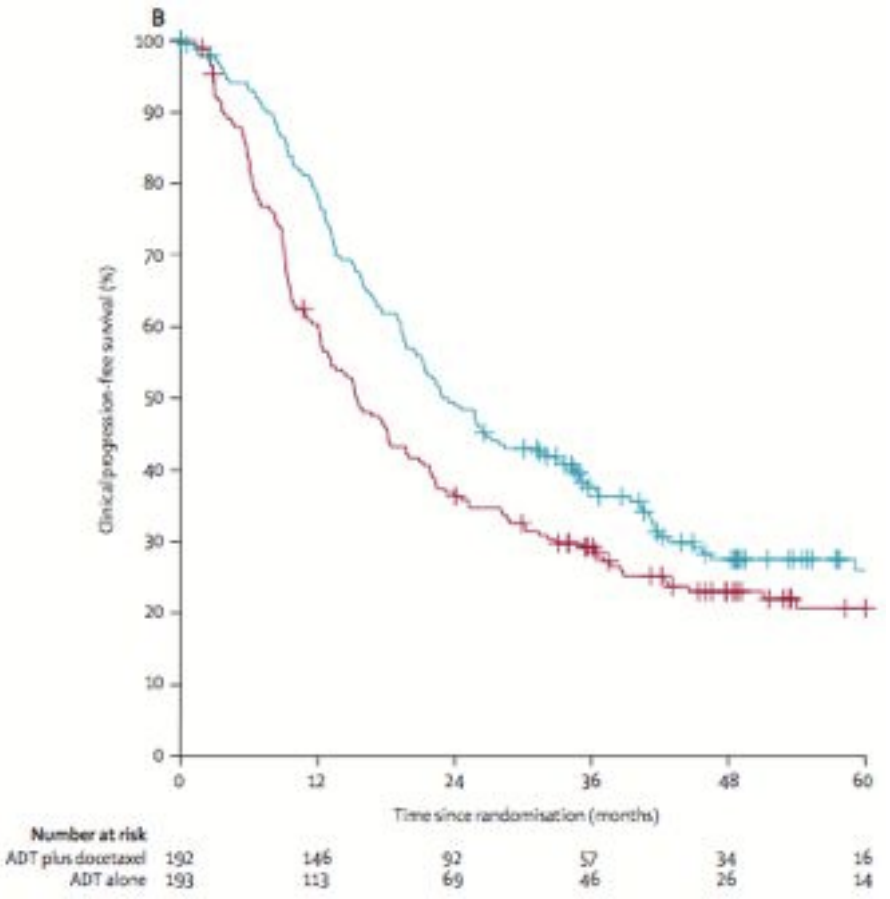


Gravis G, et al. Lancet Oncol. 2013;14(2):149-158.

GETUG-AFU 15: Progression Free Survival



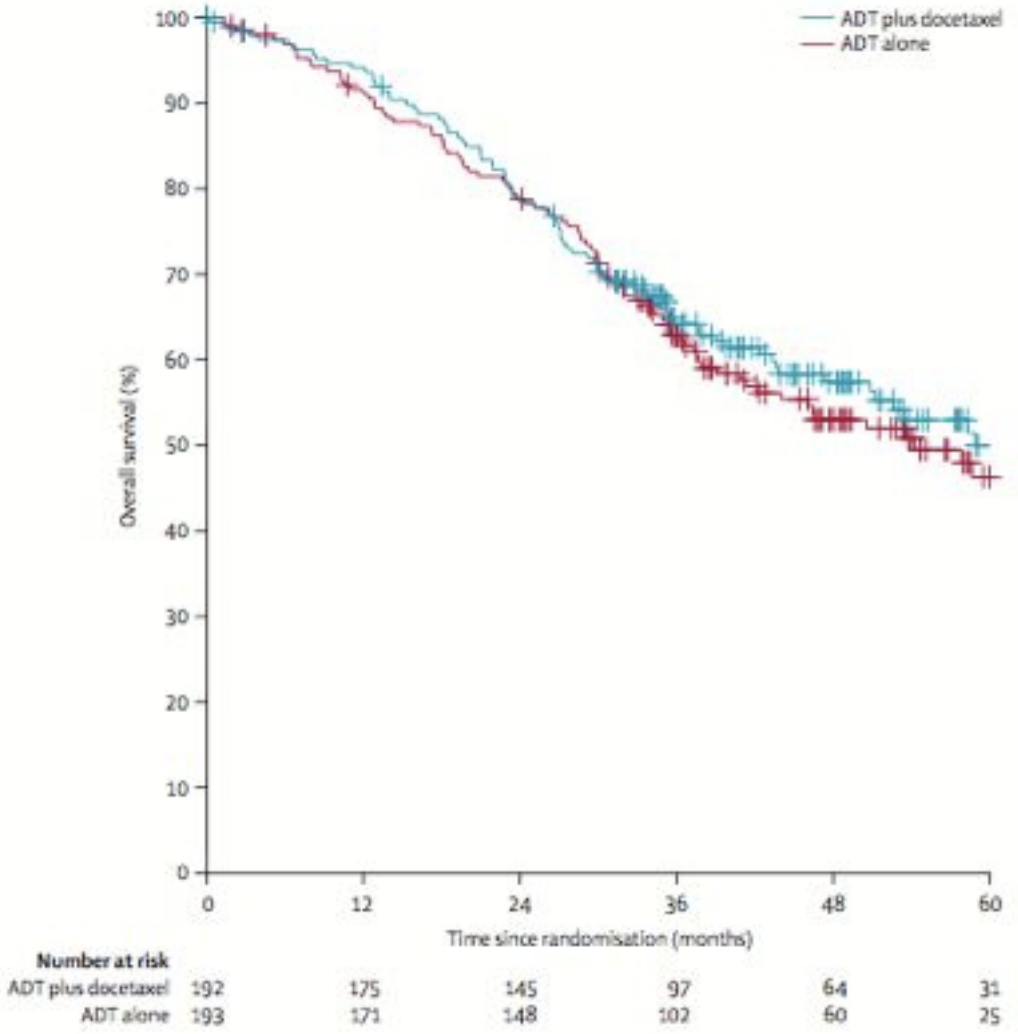
Biochemical PFS



Clinical PFS

Gravis G, et al. Lancet Oncol. 2013;14(2):149-158.

GETUG-AFU 15: Overall Survival



Docetaxel should not be used as part of first-line treatment for patients with non-castrate metastatic prostate cancer.

Gravis G, et al. Lancet Oncol. 2013;14(2):149-158.

JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes

Table 1. Summary of Recommended Targets for Meaningful Clinical Trial Goals

Cancer Type	Patient Population	Current Baseline Median OS (months)	Primary End Point: Improvement Over Current OS That Would Be Clinically Meaningful (months)		Primary End Point: Target HRs	Secondary End Point: Improvement in 1-Year Survival Rate (%)*	Secondary End Point: Improvement in PFS (months)
Pancreatic cancer	FOLFIRINOX-eligible patients	10 to 11[19]	4 to 5	40/45	0.67 to 0.69	48 → 63	4 to 5
Pancreatic cancer	Gemcitabine or gemcitabine/nab-paclitaxel–eligible patients	8 to 9[20,21]	3 to 4	37/44	0.6 to 0.75	35 → 50	3 to 4
Lung cancer	Nonsquamous cell carcinoma	13[22]	3.25 to 4	25/31	0.76 to 0.8	53 → 61	4
Lung cancer	Squamous cell carcinoma	10[23]	2.5 to 3	25/30	0.77 to 0.8	44 → 53	3
Breast cancer	Metastatic triple negative, previously untreated for metastatic disease	18[24,25]	4.5 to 6	25/33	0.75 to 0.8	63 → 71	4
Colon cancer	Disease progression with all prior therapies (or not a candidate for standard second- or third-line options)	4 to 6[26]	3 to 5	75/83	0.67 to 0.67	25 → 35	3 to 5
		CHAARTED		**17**	**53**		

Abbreviations: FOLFIRINOX, leucovorin, fluorouracil, irinotecan, and oxaliplatin; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
*Current → target.

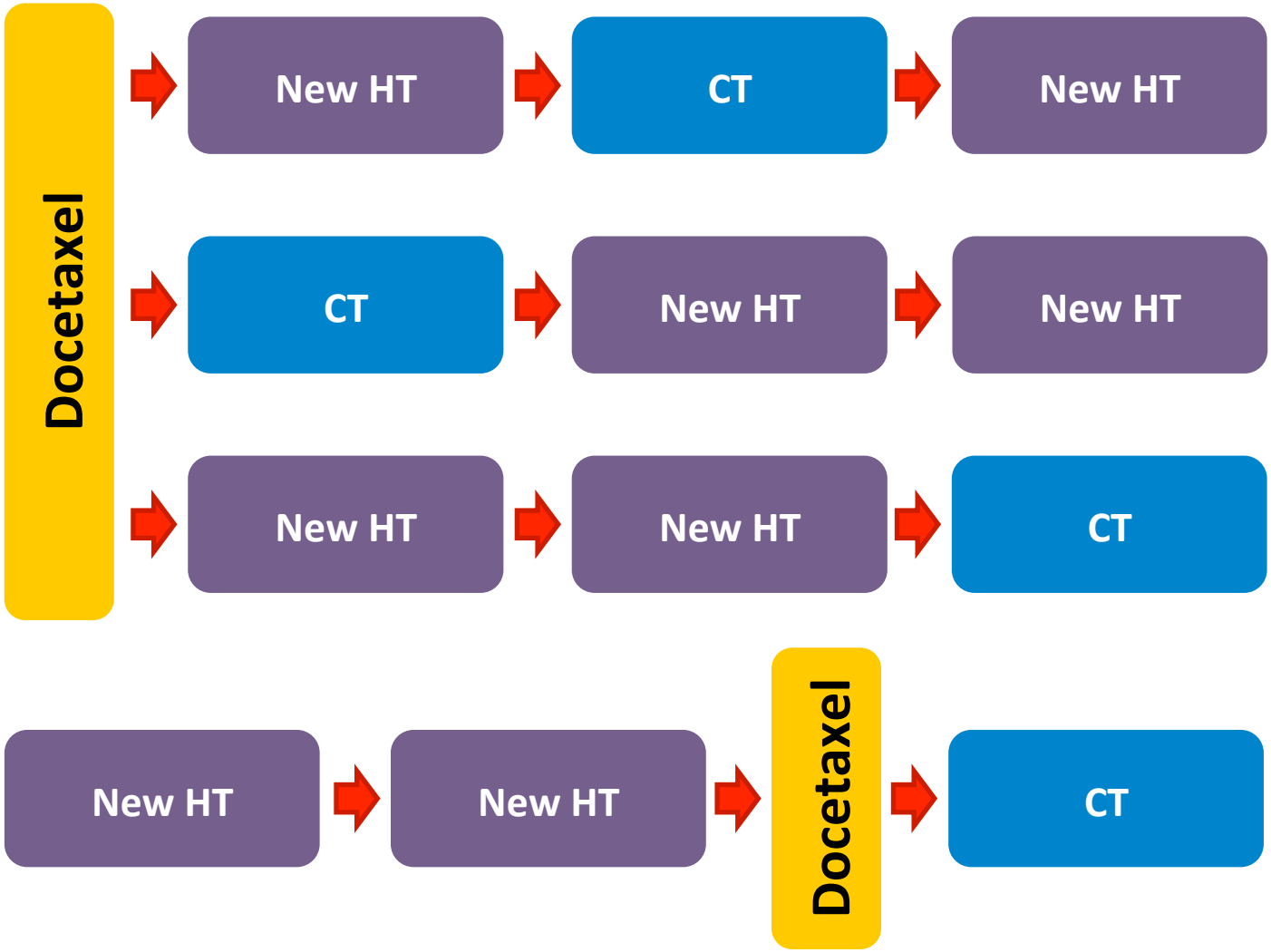
Ellis LM et al, JCO Apr 20, 2014:1277-1280

COST vs VALUE, CRPC vs CSPC

Agent	Application	Cycles	AWP for one cycle	Total Cost for a course of tx	Days gained in OS
Docetaxel q 3w	mCRPC pre-doce	10	$1500	$15,000	81.2
Abiraterone	mCRPC pre-doce	14 mo	$6836	$95,704	145
Radium-223	mCRPC post- and pre	6	$11,500	$69,000	79
Sipuleucel	mCRPC post- and pre	3	$31,000	$93,000	123
Cabazitaxel	mCRPC post-doce	6	$8600	$51,600	72
Abiraterone	mCRPC post-doce	8 mo	$6836	$54,688	117
Enzalutamide	mCRPC post-doce	8 mo	$7889	$63,112	144
Doce q 3 w	mCSPC – total pop.	6	$1500	$9,000	381
Doce q 3 w	mCSPC – high vol	6	$1500	$9,000	476

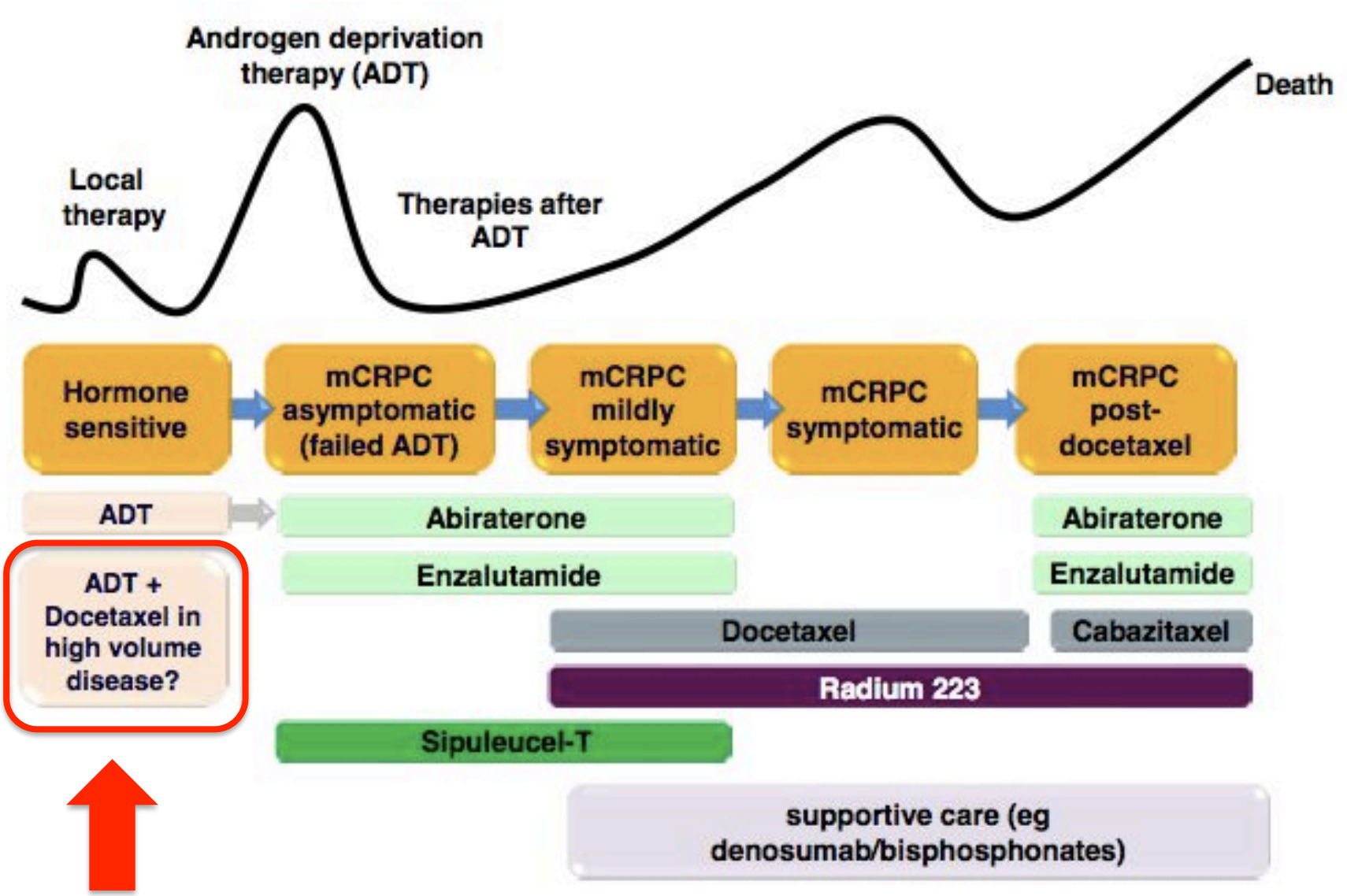
Modified by Morris MJ Discussant Plenary session June 1, 2014

mCRPC: Evolution or Revolution



Modified by Caffo O, AIOM post-ASCO 2014

Current Treatment Paradigm is Evolving



Modified by Sternberg CN, Education Prostate – ESMO 2014

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